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FATAL APNŒA AND THE SHOCK PROBLEM.[1]

By Yandell Henderson, Ph. D.,

Assistant Professor of Physiology in the Yale Medical School.

The topic upon which I shall speak is a very old one, perhaps the oldest in medicine. Yet I shall ask you to regard it from a somewhat novel standpoint. At the present time it is very easy to find novel treatments of old topics in physiology. It is not necessary to discover new material. One need only look at the data of normal physiology from the standpoint of the abnormal. With little labor on his own part the abnormal physiologist of to-day may draw dividends upon the capital accumulated by the normal physiologist in the past, especially in that field to which I shall invite your attention this evening.

This field of physiology is comparable to one of those mines in Austria from which came ore yielding uranium. For many years only the uranium was extracted and the residue of the ore after this extraction was thrown upon the waste heap. At last it was discovered that this waste was rich in radium and the heaps of material hitherto worthless became again immediately of great value. So it is in my topic. Physiologists in the past have dug out of the depths immense amounts of material. From this they have extracted theories and explanations of the normal, but they have quite generally neglected to work out those elements which would be of practical usefulness. They have, I fear, been even a little scornful of those who have descended from the heights and have offered their material as useful to the clinician. That which I shall attempt consists merely in extracting some principles of abnormal function and, as I hope, of practical and applicable clinical usefulness from the heaps of material accumulated by previous physiologists.

During the past hundred years an immense amount of work has been done in the field of respiration. From this material numerous investigators have extracted every particle of in-

[1] Read before the Johns Hopkins Hospital Medical Society. December 6, 1909.

formation bearing upon the problem—How and why do we breathe? I have attempted to extract from this same material the answer to the question—How and why do we stop breathing? As every one of us will some day stop breathing, even a partial answer to the latter question appears well worth extracting.

The simplest and clearest cases of fatal apnœa are those which occur after intense pain. In order to bring my particular problem clearly before you, I will instance a case. A man in the prime of life was setting off fireworks on the evening of the last Fourth of July when a giant firecracker exploded in his hand and shattered it. There was no considerable loss of blood. For two hours he suffered intensely, although he received a quarter of a grain of morphin. Then anæsthesia with ether was attempted, and his breathing immediately began to fail. The anæsthetic was withdrawn, and respiration improved. Three hours after the accident he stopped breathing quite suddenly. Artificial respiration and stimulants were ineffective, and he died. Yet his pulse was fairly good before and even for some minutes after respiration ceased. Why did that man die?[2] In order to make the further discussion of my topic clear I will present immediately the explanation to which, as it seems to me, all the data point. During the period after the accident his breathing was of the type which insupportable pain always excites. This hyperpnœa involved a far greater ventilation of the lungs than normal breathing affords. Consequently the CO_2 content of the blood, and finally also of the body as a whole, was greatly diminished. When anæsthesia was attempted it was almost inevitable that respiration should show signs of failure. CO_2 is the normal stimulant of respiration; therefore, after this normal chemical stimulant to breathing had been reduced, pain alone maintained the breathing. Anæsthesia removed the pain. Finally breathing stopped for the very simple reason that there was not enough CO_2 left in the blood to excite the respiratory center to activity. To this condition of diminished CO_2 content in the blood Mosso has given the name "acapnia" from the Greek "kapnos," smoke. Literally, acapnia means smokelessness. Perhaps I should remind you that the arterial blood normally contains 20 volumes per cent of oxygen, and 40 of CO_2; and that the body as a whole has an enormously greater store of CO_2 than of oxygen.

Before I proceed to explain the experimental basis for this long range diagnosis, I wish briefly to consider the question whether this was a case of surgical shock. The condition to which the surgeons apply this name has been defined by Crile as consisting essentially in a low arterial pressure. Early in my investigations upon traumatic shock I was met by an unexpected difficulty. At first I tried to produce shock as Crile had done by exposure and irritation of the abdominal viscera. To my surprise, the dogs upon which I worked usually died of failure of respiration long before arterial pressure had fallen to such an abnormally low level as would accord with Crile's definition. All modern work upon shock must take its starting point from the investigations of Crile, splendid as they are in extent and thoroughness. Accordingly, I reread Crile's work with this point in mind, and I found that his experience had been precisely the same as my own. Crile says that "in 103 of the experiments in which the exact manner of death was recorded, or in which in the course of the experiments the heart or respiration failed first, respiration alone failed in 90, the heart alone in 4, and both simultaneously in 9. In many instances the heart was beating strongly and the blood pressure was fair at the time respiration failed." In many of Crile's experiments he was obliged to employ artificial respiration in order to keep his animals alive until the low blood pressure developed. Otherwise, as this quotation shows, nearly all of his animals would have died of failure of respiration. I do not desire to alter Crile's definition of surgical shock as "low blood pressure." I would apply the name "fatal apnœa vera" to the death of the man of whom I spoke, and to the failure of respiration observed by Crile in the dogs of his experiments and in the animals employed in my own. All that I contend is this: After intense pain, but in the absence of hemorrhage, death usually results from failure of respiration before arterial pressure has fallen to a dangerous level. Under experimental conditions it is really difficult to induce a condition meeting Crile's definition. It is necessary that the subject should be watched very carefully and that every time respiration begins to fail some afferent nerve should be irritated so vigorously, that apnœa is prevented, and the respiratory center is forced into renewed activity. By conforming with this precaution, however, I have succeeded in inducing typical surgical shock in some 20 animals. It was my good fortune to have Dr. Crile as a witness of one of them, so that when I use the term "Surgical Shock," I mean the real thing—the shock of Crile.

I shall not attempt in the brief time at my disposal to analyze in detail this condition of low arterial pressure. I may say, however, that I do not believe it is due to fatigue or inhibition or failure of any sort in the vasomotor center. On the contrary, that center does its full duty almost to the last. It is like the Roman legionary at the gate of Pompeii, who stood at his post until overwhelmed by the ashes of Vesuvius. In less figurative language the fact is that the small arteries are contracted, not relaxed, during the stage of low arterial pressure, as Malcolm in England, and Seelig and Lyon in this country have shown. The failure of the circulation appears rather to be due to diminution in the volume of the blood by transudation of its fluid out of the vessels into the tissues, a process like edema. It is a complex peripheral process induced initially by the influence of acapnia upon the veins and capillaries and upon the tissues. Thus when death follows intense physical suffering, not complicated by hemorrhage, there are two principal stages. At first, the excessive breathing diminishes the CO_2 content of the blood. If at any time after this condition of acapnia has been induced the pain is greatly diminished and the respiratory center is thus allowed to relapse into a standstill, fatal apnœa vera may occur. If, on

[2] It has been suggested to me that the "toxins of roasted tissue" were a factor in the case. On the contrary, however, the burns inflicted were very slight.

the other hand, the pain is sufficiently continuous to keep the respiratory center continually excited then apnœa is prevented, and the condition of acapnia becomes more and more acute and general until the circulation fails, and the subject sinks into surgical shock according to Crile's definition. Both fatal apnœa and the more slowly developing failure of the circulation are due initially to acapnia induced by the excessive breathing occurring under torture.

So much for the point of view of an advocate of the acapnial hypothesis of surgical shock. It will next be necessary for me to attempt to show you how these somewhat heterodox views can be derived quite logically, I believe, from the orthodox doctrines of normal physiology.

The textbooks used to tell us that there were four factors involved in the maintenance of normal breathing. First, an automaticity of the respiratory center similar to that of the heart;[1] second, afferent nerve influences, especially those induced through the vagi from their sensory endings in the lungs; third, the need for oxygen; fourth, the excess of CO_2 in the blood.

The first of these factors has been proved by the investigations of the last ten years to be non-existent. A perfectly normal center, such as mine now is, will come to a standstill the instant it ceases to be driven. It is so pitilessly lazy that it will let its owner die if it is not whipped or spurred into a renewal of activity. The respiratory center, therefore, is not automatic in the sense that it will run of itself.

On the second factor it has become increasingly evident that, although the center is responsive to afferent nervous impulses, it is thus influenced only in the same manner as a clock is influenced by the length of its pendulum. The force corresponding to the spring or weight in a clock is afforded by chemical conditions in the blood. Variations in afferent impulses reaching the respiratory center induce alterations in the form of breathing, especially in its rate, as the pendulum regulates the ticking of a clock, but they have little influence, under ordinary conditions, upon the total pulmonary ventilation. Thus to take an illustration, in myself at the present time my respiratory center, in inducing the sounds which you hear, is subject to a flow of nervous stimulations. Yet the total rate at which my lungs are being ventilated is not thereby altered from the rate at which they would be ventilated were I not speaking. The ticking of my respiratory clock is different under the two conditions, but the rate at which the weight falls or the spring unwinds, or in other words, the rate at which CO_2 is eliminated, is dependent upon the respiratory needs of my body.

Perhaps there is no idea more firmly fixed in the medical mind, or which it will be harder to root out, than the idea that the respiratory center is sensitive to alterations in its oxygen supply. Yet during the past few years it has been conclusively demonstrated that within wide limits the respiratory center is wholly indifferent both to excess and to lack of oxygen. It should be added, however, that this statement needs modification so as to admit that conditions which result from anoxhæmia do irritate the center. These conditions, however, are produced slowly and in the tissues, not primarily in the center. Even to a total lack of oxygen the respiratory center makes no immediate response, although it may be killed thereby. Thirty years ago that brilliant Swiss investigator, Miescher, expressed the essential truth regarding the regulation of normal breathing in these words: "Over the oxygen supply of the body CO_2 spreads its protecting wings." The form of death from respiratory failure of which I have been speaking is very simply explained as due to the withdrawal of these "protecting wings." After they are withdrawn death ensues from lack of oxygen.

The crucial experiment in this field is that of voluntary forced breathing. The experiment is so simple and so easily performed at any time by anyone that it ought to become universally familiar. It is only necessary to breathe as rapidly and as deeply as you can, taking care that you do not inspire with the diaphragm while expiring with the costal muscles. Keep this up for one or two minutes, or if you have the courage, for five or ten minutes. Thereby you will induce in yourself a moderate degree of acapnia. When you cease the voluntary effort you may find that your hands are temporarily paralyzed. Your legs and arms may be asleep. You may shiver as in a chill. You will feel strangely lightheaded. Breathing exercises are no new thing. They have been practiced for three thousand years by the Buddhist monks of India. Some of those American cranks who have taken up the so-called Yoga philosophy and practice breathing exercises attain such a degree of mental exaltation and light-headedness after forced breathing that they feel themselves literally lifted from the ground and floating in the air. I have never myself quite left the floor, but once or twice I have felt as if I were going to. The main point in performing this experiment, however, is this: If your efforts have been sufficiently energetic and a considerable degree of acapnia has been induced, when you stop forcing yourself to breathe, you will stop breathing altogether. In this respect the respiratory center is entirely automatic. If you have previously reduced your store of CO_2 sufficiently, you will remain breathless and without any desire to breathe, until you turn blue in the face. It is not at all improbable that a man could thus commit suicide.

This form of respiratory failure is termed apnœa vera, or true apnœa. That acapnia is the cause of apnœa vera has been demonstrated by Haldane and Priestley. They have shown that it is quite easy to catch the last of the air expired in a deep expiration, and that this air is the alveolar air of the lungs. Upon themselves and others they have performed a long series of analyses of the alveolar air. They find its composition in respect to the CO_2 tension to be extraordinarily constant. In the depths of a Welsh mine or on the summit of a mountain, with a variation in atmospheric pressure of several hundred millimeters of mercury, the respiratory center automatically maintains the alveolar tension of CO_2 constant to within a fraction of 1 per cent. On the other hand, under these varying conditions the oxygen tension in the lungs varied

[1] Foster, M.: A Text-Book of Physiology, 1895, pp. 371-2.

by more than one-third without the activity of the respiratory center being thereby in the least degree modified. When a man breathes pure oxygen Haldane has shown that his respiration continues to be controlled solely in relation to the CO_2 elimination. The addition of 0.2 per cent CO_2 to the air automatically doubles a man's pulmonary ventilation.

Recently Haldane and Poulton offered a demonstration before the British Physiological Society in which Poulton performed forced breathing for two and a half minutes. Then he lapsed into apnœa. After a couple of minutes his face assumed a leaden corpse-like appearance characteristic of great anoxhæmia. Yet it was a full minute after this before he experienced any desire to breathe. Several of the British physiologists in the audience were so upset by the spectacle that they could scarcely be hindered from performing artificial respiration upon him. One or two were obliged to leave the room.

Such experiments as these, and they have been repeated sufficiently often to assure their correctness, demonstrate conclusively that lack of oxygen itself is not a stimulant to the respiratory center. After the oxygen supply of the blood, lungs, and tissues has been exhausted,—and this in such a case as that of Poulton appears to occur in two or three minutes,—the asphyxia of the tissues results in the appearance in the blood of the products of incomplete tissue combustion. This is a form of acidosis. The acidosis bodies stimulate the respiratory center, or rather add their stimulating influence to that of the CO_2 remaining in the blood. Thus, after a short period of forced breathing, apnœa lasts until the CO_2 has reaccumulated in the blood up to the normal amount—that is up to the threshold stimulating value for the respiratory center. But after more prolonged forced breathing and apnœa lasting until acidosis results, the breathing recommences while the CO_2 content of the blood is still below normal. In experiments of this character Haldane and Douglas have found a beautiful explanation of Cheyne-Stokes breathing. A man after prolonged apnœa starts to breathe because of the combined influence of the acidosis bodies and of the CO_2 remaining in his blood. The first few breaths, or even the first breath, supplies sufficient oxygen to oxidize the acidosis substances; and the subject lapses into apnœa. The repetition of this cycle affords typical Cheyne-Stokes breathing in a perfectly normal man.

The influence of acidosis in shortening apnœa, and thus preventing death from asphyxia, is illustrated by an experiment by Vernon. He finds that without forced breathing he can hold his breath for less than a minute. After forced breathing he can hold it three or four minutes. After forced breathing ending with two or three inhalations of oxygen he has held it for eight minutes and thirteen seconds. This is at present the record, and one which I personally have no desire to beat.

The experiments of my collaborators and myself in this field are in part already in print, in part they are now in the hands of the printer, and the remainder will appear within a couple of years. I will not, therefore, burden you with their details, but I will briefly run over their essential points. In one series of experiments the thorax of the dogs on which we worked was opened and the animals were maintained under artificial respiration. The operation was so severe that if trauma or irritation of afferent nerves in and of itself were the cause of shock all of the animals should have passed rapidly into this condition. It was found, however, that actually the sole condition determining the rate at which the animals sank into shock was the pulmonary ventilation. If we did not give them too much air, the circulation was maintained at a normal pressure for many hours. If, on the other hand, the pump with which artificial respiration was supplied was worked a little too vigorously, the animals sank rapidly into shock. Thus excessive artificial respiration affords a means of inducing a condition closely similar to, if not identical with, that induced by pain.

In another series of experiments the abdominal viscera were exposed, handled and aerated. This, of course, induced continuous hyperpnœa. I should say parenthetically that all of the animals in these experiments were anæsthetized or otherwise drugged to the point of complete unconsciousness. It is not the consciousness of pain, but the effect of pain (*i. e.*, intense afferent irritation) upon the respiratory center which induces acapnia and shock. In these particular experiments in which the abdominal viscera were thus treated both the arterial and the venous blood were analyzed for their gases. It was found that the development of shock fell into two stages. At first, the CO_2 content of the arterial blood diminished gradually, the oxygen content remaining unaltered. During this process the oxygen content of the venous blood steadily diminished until finally the blood in the large veins was totally deficient in oxygen. When this stage was reached the tissues did not receive enough oxygen to meet their respiratory needs. If irritation of the viscera was stopped prior to this complete venous anoxhæmia, fatal apnœa occurred. After this time fatal apnœa was less likely to occur, but the volume of the blood stream appeared to diminish steadily. This, as I have already suggested, I believe to be due to the alteration in the respiration of the tissues, to the development of tissue asphyxia and of acidosis, and to the consequent transudation of the fluid of the blood into the tissues. I believe that this process is one of imbibition or absorption of water by the colloids of the protoplasm of the tissue cells,—a process similar to the swelling of fibrin in dilute acids. The details of this process, however, still require a great deal of work for their complete elucidation.

In two other sets of experiments we have attempted to compare the effects of excessive artificial respiration with the effects of intense afferent irritation. Their object was to see to what extent the after-effects of trauma are due to the acapnia resulting from the hyperpnœa. For the former we used two large automobile tire pumps, one of which forced air into the lungs while the other withdrew it. When a dog is subjected to this treatment for 20 or 30 minutes and then left to himself, he lies perfectly quiet without attempting spontaneous breathing for many minutes. In the more successful experi-

ments the subjects have lain perfectly quiet until in eight minutes their hearts failed for lack of oxygen.

In the other and comparable set of experiments the animals were forced to supply their own excessive pulmonary ventilation. The sciatic nerves were dissected out and stimulated for 20 to 30 minutes. Thereby a vigorous natural hyperpnœa was maintained. When the stimulation was discontinued the animals ceased to breathe altogether and in the more successful cases lay perfectly quiet until after eight minutes when their hearts failed for lack of oxygen. The two sets of experiments have afforded results so nearly concordant that it is difficult to distinguish between them. Apparently in these cases at least all of the after effects of pain are explicable as due to the acapnia which pain (*i. e.*, the breathing of pain) induces. Apparently if Torquemada had administered the tortures of the Spanish Inquisition in an atmosphere of 5 or 6 per cent of CO_2, while the sufferings of his victims would not have been less, they would not have developed surgical shock. Certainly thereafter they would not have died of fatal apnœa.

Those cases of fatal apnœa which more than any other interest the clinician are, I suppose, the failures of respiration under anæsthesia. If the patient ceases to breathe in his bed it is his own fault, but if he does so on the operating table the anæsthetist has to bear the responsibility. For such cases of apnœa the acapnia hypothesis affords a simple explanation. Anæsthesia diminishes the strength of inflowing afferent irritations. Furthermore profound anæsthesia raises the threshold of the respiratory center for CO_2. In other words, the respiratory center of a man or animal in profound anæsthesia automatically maintains more than the normal CO_2 content in the blood. Thus when a man or woman or child has suffered prolonged pain and thereby has been brought into a condition of more or less acapnia, the production of anæsthesia by removing the afferent pain stimuli, and also by raising the threshold, that is by diminishing the sensitiveness, of the respiratory center for CO_2 inevitably leads to apnœa.

This, however, is not quite the whole story. When I first tried to produce fatal apnœa I kept the dogs upon which I worked under ether alone without morphin. The experiments failed. Either the animals exhibited no apnœa or only a very brief period of respiratory standstill. In some cases after prolonged artificial respiration or intense stimulation of afferent nerves, although a considerable degree of acapnia had been induced, the subjects continued to breathe and even to breathe excessively. After a great deal of trouble it has finally appeared that this was due to nothing more nor less than the well-known influence of ether as a respiratory stimulant. As a rule dogs are quite prone to that peculiar phase of anæsthesia called "ether excitement." In this condition we find that the respiratory center will spontaneously and without afferent irritation maintain a hyperpnœa sufficiently vigorous to produce acapnia.

In this connection I remember one of my bitterest disappointments. A fine strong dog of irritable temper had been given me by a friend for an experiment in which acapnia was the last thing wanted. I attempted to bring the dog under ether. He fought, breathed violently, came part way under the influence of the anæsthetic, and then out again. Finally I succeeded in getting him quiet, and immediately he stopped breathing. My utmost efforts failed to induce him to breathe again. This was before I knew that an animal can breathe too much. Nothing whatever had been done to this animal except to induce acapnia by means of ether excitement, and then to induce apnœa by restoring the threshold of the respiratory center to its normal level by full anæsthesia.

Now a few words on prophylaxis. The acapnia hypothesis requires the prevention of excessive pulmonary ventilation. The administration of morphin and full anæsthesia diminish the activity of respiration under pain and thus prevent acapnia. If, however, you administer morphin or chloroform to a subject after he has suffered for some time, you hasten fatal apnœa, unless you administer CO_2 also. In India, according to Lauder Brunton, it is customary to partly smother a man who has been severely injured. It would probably be wise when a man's legs have been crushed in a railroad accident to hold a paper bag over his nose and mouth so that the excessive respiration of pain might not induce acute acapnia. In experiments in the laboratory we have found that when forced respiration is performed into a paper bag the excessive ventilation of the lungs is prevented and the subject at the end of the hyperpnœa, instead of passing into apnœa, continues to breathe normally. The same result may be accomplished by breathing through a tube. We have employed a piece of single tube bicycle tire, three to five feet in length. For the most part, however, the prevention of shock, even if the acapnia hypothesis prove true, will still consist in the prevention of pain.

On the topic of the therapy of shock, which the acapnia hypothesis suggests, I have carried out as yet only a few experiments. When a moderate degree of shock has been induced by irritation of afferent nerves or by exposure of the viscera, I find that it is possible to induce a rapid recovery of arterial pressure by the infusion into a vein of normal saline or of Ringer's solution saturated with CO_2. Then the animal is made to breathe an atmosphere of oxygen and CO_2 or else merely of oxygen supplied at the end of a long tube. Under these conditions it rebreathes the oxygen several times and thus the CO_2 which the subject itself produces is utilized to stimulate respiration and increase the otherwise insufficient oxygen intake. If the degree of shock previously induced is not too severe, not only do these measures of relief induce a rapid restoration of arterial pressure and respiration, but this restoration is maintained. On the other hand, in profound shock these measures fail to effect an ultimate recovery. Indeed, after the diminished blood stream has resulted in tissue asphyxia and acidosis no measure of relief, except perhaps hypertonic saline solution or transfusion of blood, can be of much use.

There are two methods of treating acapnial failure of respiration under anæsthesia. We find that if a soft catheter is inserted in the trachea down to the bifurcation of the bronchi and a gentle stream of oxygen gas is supplied, according to the

method devised by Volhard, the subject will lie for a very long time indeed in complete apnœa. By this method a supply of oxygen ample for all the needs of the tissues may be maintained. The oxygen should, however, be measured, and for a man should be not less than 400 cc. per minute. Under these conditions in animals reaccumulation of CO_2 proceeds relatively rapidly. In one case I have seen a dog in acute acapnia lie for 12 minutes without the slightest respiratory effort and at the end of this period recommence normal breathing. The oxygen jet had supplied ample oxygen for the combustion of the acidosis substances which would otherwise have been produced. This method of Volhard, therefore, accomplishes a double object. It prevents the acidosis of asphyxia at the same time that it allows the subject to recover from acapnia. I do not know whether surgeons would be willing to utilize it in the operating room. It requires some courage to leave a patient perfectly quiet and breathless—much more courage if it is a man than if it is a dog.

Another method of restoration of breathing has been tried upon dogs during apnœa with strikingly successful results. It consists in administering air or oxygen containing 5 or 6 per cent of CO_2 and in starting the subject to breathing by one or two artificial respirations. As soon as the normal tension of CO_2 in the lungs is thus restored spontaneous breathing immediately recommences and is maintained as long as the inspired air contains a sufficient quantity of CO_2 to stimulate the respiratory center. It will, I think, be advisable to use for this purpose oxygen and CO_2, and not merely air plus CO_2, for the purpose of preventing the acidosis of which I have spoken. Indeed, oxygen and CO_2 would combine the advantages of both methods for preventing fatal apnœa. It must be remembered that CO_2 is a powerful drug and one to be administered in small quantities only—never in greater concentration than 5 or 6 per cent. I have devised a simple gas meter which I believe may be useful for measuring the small quantities of CO_2 to be added to air or oxygen as a respiratory stimulant. It would be better to have the gases already mixed. I hope to be able to induce the manufacturers to supply tanks of oxygen containing 5 or 6 per cent of CO_2, and I hope to be able to persuade clinicians to use it.

This brings to a close what I fear is both a superficial and obscure presentation of the acapnia theory of fatal apnœa vera and of shock. I do not myself regard this theory as yet as anything more than a working hypothesis. I accepted gladly the invitation from your secretary to present it to you this evening because I felt that in this audience I should find men fitted to point out the shortcomings in the theory. I understand that it is your custom to discuss the papers which are presented before you. I assure you that I will appreciate it very highly as a great help to me in the final working out of this theory if you will now criticise it as severely as you possibly can—the more severely the better.[1]

[1] For the experimental data and references to the literature on which this paper is based see the American Journal of Physiology, 1908, XXI, p. 126; 1909, XXIII, p. 345; 1909, XXIV, p. 66; 1910, XXV, p. 310, and p. 385; 1910, XXVI, p. 260. On the clinical side of the subject see the paper of Malcolm, J. D.: Transactions of the Medical Society of London, 1909, XXXII, p. 289; and Gatch, W. D.: Journal of the American Medical Association, 1909, LIV, p. 775.

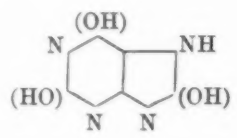
ON THE THREEFOLD PHYSIOLOGICAL ORIGIN OF URIC ACID.*

By Walter Jones, Ph. D.,

Professor of Physiological Chemistry, Johns Hopkins University.

The uric acid of the urine is produced by three physiological processes which so far as we can see are not directly dependent upon one another. It is therefore necessary that in any discussion of the abnormal production of this substance, due consideration be given to all three sets of conditions under which it normally makes its appearance in the body. One of these processes is known as the nuclein metabolism and is concerned with the nucleic acids which constitute a large part of the material present in the nuclei of all cells. For a clear understanding of the nuclein metabolism it is advisable to discuss some matters of chemical structure.

The constitution of uric acid was established by a synthesis of Behrend (1), who proved that the substance is correctly represented as the trioxy derivative of a double ring consisting of a pyramidin ring and an imidazol ring united in the manner indicated in the formula



Starting with the uric acid of known constitution Fischer (2) prepared a substance having three chlorine atoms in place of the three hydroxyl groups and from this chlorine substitution product a large number of derivatives were prepared, including the mother substance of them all. This mother substance is called purine and the numerous compounds which Fischer prepared from its trichlor substitution product are known as purine derivatives. Four of them, viz., guanine, adenine, xanthine and hypoxanthine, are of great importance in dealing with the physiological origin of uric acid. Their relation to one another and to uric acid is shown in the follow-

* Paper read before the Johns Hopkins Hospital Medical Society, April 18, 1910.

ing diagram in which purine with its three replaceable hydrogen atoms would be represented by

$$P\begin{cases}-H(2)\\-H(6)\\-H(8)\end{cases}$$

Guanine (2-amido-6-oxypurine)	Adenine (6-amidopurine)
$P\begin{cases}-NH_2(2)\\-OH\ (6)\\-H\ \ (8)\end{cases}$	$P\begin{cases}-H\ \ (2)\\-NH_2(6)\\-H\ \ (8)\end{cases}$
↓	↓
Xanthine (2-6-dioxypurine)	**Hypoxanthine (6-oxypurine)**
$P\begin{cases}-OH(2)\\-OH(6)\\-H\ \ (8)\end{cases}$	$P\begin{cases}-H\ \ (2)\\-OH(6)\\-H\ \ (8)\end{cases}$
←	←
Uric Acid (2-6-8-trioxypurine)	
$P\begin{cases}-OH\\-OH\\-OH\end{cases}$	

It will be seen that adenine contains an amido group where hypoxanthine contains a hydroxyl group: otherwise the structure of the two substances is the same. It should, therefore, be possible to convert adenine into hypoxanthine. As a matter of fact the transformation can easily be accomplished: indeed the discoverer of adenine (Kossel) thus proved its relation to hypoxanthine (3). Not only can adenine be converted into hypoxanthine, but the experimenter must be constantly on his guard lest the transformation occur in some analytical procedure without his intention or even without his knowledge and thus lead to false conclusions.

The chemical relation of guanine to xanthine is the same as that of adenine to hypoxanthine; guanine and adenine are amido purines, xanthine and hypoxanthine the corresponding oxypurines. In both cases the amido compound can be converted into the oxycompound, water being taken up and ammonia liberated according to the general equation

$$R.NH_2 + H_2O = ROH + NH_3.$$

This reaction, in the most general sense of the term, is hydrolysis, but as it is not brought about by boiling acids it is more commonly known as disamidization.

Uric acid is a simple hydroxyl derivative of xanthine and xanthine likewise of hypoxanthine. By oxidation under proper conditions it is possible to convert hypoxanthine into xanthine and this in turn into uric acid. But it is necessary to observe that while the empyrical chemical relation of guanine to adenine is the same as that of xanthine to hypoxanthine, there is a structural difference between the two former which makes it impossible that one of these substances be directly converted into the other. While hypoxanthine can be directly oxidized to xanthine, adenine cannot similarly yield guanine, but would yield 6-amido-2 oxypurine. This by further oxidation might be expected to produce 6-amido-2-8-dioxypurine which by disamidization could pass into uric acid. Thus uric acid may theoretically be formed:

1. From adenine through hypoxanthine.
2. From adenine through 6-amido-2-8-dioxypurine.
3. From guanine through xanthine.

Other obvious theoretical possibilities do not concern us.

The physiological importance of these relations becomes apparent when it is stated that all nucleic acids, whether of plant or animal origin, yield equivalent quantities of guanine and adenine upon hydrolysis with boiling mineral acid (4). While this statement is rigidly correct, it is not in accordance with the results of the older experimenters, who found four purine derivatives among the hydrolytic products of nucleic acid. This apparent discrepancy has been brought about by a number of factors. In the first place, the method of hydrolysis employed in the older work was of such a nature that one can see how the two amidopurines first formed would of necessity be partly transformed into the oxypurines; but so far as concerns guanine it has been shown that when hydrolysis of nucleic acid is effected by ferment action at the body temperature and in a practically neutral fluid, there is no formation of the oxypurine (5). Again, there is a wide occurrence in the body of a substance called guanylic acid which yields guanine but not adenine. This substance is not to be regarded as a nucleic acid and its presence in various nucleic acid preparations has undoubtedly led to confusion in the relative quantities of guanine and adenine which nucleic acids produce (6). Lastly, there is considerable reason for supposing that the nucleic acid material employed by the older workers actually contained oxypurines as impurities. At any rate the concordant results of all modern investigations prove beyond question that nucleic acids, when properly prepared and hydrolyzed, yield equivalent amounts of guanine and adenine but no other purine derivative.

It has been repeatedly shown that when nucleic acid is submitted to the action of aqueous glandular extracts at the body temperature, the substance undergoes hydrolysis with the production of the purine derivatives guanine and adenine. As the hydrolytic agent in these extracts is destroyed by heat, varies in the extent of its action directly with time and possesses the attributes of a number of other active physiological agents, it is looked upon as ferment and has received the name "nuclease" (7). It has also been demonstrated that the two amidopurines (guanine and adenine) are converted into the two corresponding oxypurines (xanthine and hypoxanthine) by the action of thermolabile active agents present in the aqueous extracts of various glands (8). As the extracts of certain glands promptly disamidize relatively large quantities of one of the amidopurines but exert little or no action on the other, the conclusion has properly been drawn that two independent active agents are concerned in the disamidization, viz., "guanase" and "adenase" (9). Again, certain glands contain an active agent under whose influence hypoxanthine and xanthine are oxidized to uric acid. This oxidizing ferment, known as xanthoöxidase (10), is of course capable of exerting its action only in the presence of a proper supply of oxygen (air). Finally, when uric acid is digested at the body temperature with certain glandular extracts, the substance disappears, being probably converted into allantoin (11), which can be easily excreted.

Thus by the successive action of five independent physiological agents nucleic acid may be made to produce uric acid

and the latter be destroyed. These active agents have for sufficient reasons been called ferments, and are known specifically as nuclease, guanase, adenase, xanthoöxidase and uricase. With very rare exceptions all five of these nuclein ferments are not present in any one gland. Pig's liver exhibits xanthoöxidase to a marked degree, adenase much less so and guanase not at all, while pig's spleen promptly changes adenine into hypoxanthine, but exerts no action whatever upon guanine or hypoxanthine. Pig's spleen can disamidize adenine but not guanine (12). On the contrary, rabbit's liver can disamidize guanine but not adenine. This "distribution" of ferments is not only different for different glands, but varies to an unmistakable degree with animal species (13), a matter set forth in the following self-explanatory diagram, where solid lines are intended to indicate the presence of a ferment, dotted lines its probable absence or slight activity. The question considered is the distribution of the nuclein ferments in the livers of four animal species.

Thus the ox liver can convert into uric acid all purine material formed from nucleic acid, the rabbit's liver only one-half, the pig's liver the other half, while the dog's liver seems incapable of forming uric acid from any purine precursor (12). Such a variation with species clearly suggests that the distribution varies in each species with age. This has been proven in a number of cases. Thus the ferments of pig's liver do not simultaneously appear, but at a certain stage of embryonic development adenase can be shown before xanthoöxidase has made its appearance (14). So also one of the most active ferments of the adult human body (guanase of the liver) is not present in the embryo (15).

This great variation of purine ferments with animal species makes it necessary to find the distribution in the case of man. The difficulty of such an investigation is apparent; one cannot easily get possession of normal human organs. It occurred to us that some idea of this question might be gotten by examining a large number of pathological cases and noting the constant factors. While this work was in progress a publication appeared by Schittenhelm and Schmid (16), stating that all human organs contain all five of the nuclein ferments. The presence of uricase in the liver was specially noted. Uric acid was introduced into aqueous extracts of the organ and air passed into the material as it digested at the body temperature. After the digestion uric acid could not be found and as the method employed was such that the substance if present could not escape detection Schittenhelm and Schmid did not hesitate to announce that human organs are well supplied with uricase, which normally brings about the destruction of part of the uric acid formed from the nuclei.

From chemical experiments with gouty patients, Schittenhelm and Brugsch (17) subsequently formulated their widely known theory of gout. Divested of its unessentials, this theory is to the effect that in gout there is a disturbance of the normal activity of the ferments of the nuclein metabolism and especially of uricase the ferment that causes the destruction of uric acid; so that while normally a portion of the uric acid formed in the body is converted into products that are soluble and easily excreted, in gout the absence of uricase must lead to a condition in which uric acid becomes excessive and is laid down in the tissues. Shortly after the announcement of the Brugsch-Schittenhelm theory, the organs of a gouty patient who died in this hospital were placed at our disposal. Attention was naturally directed to the question of uricase in the liver. Aqueous extracts of this organ were digested with uric acid under conditions well adapted to the activity of uricase, but in spite of all efforts to bring about its destruction, the uric acid could be recovered unchanged. We were, therefore, of the opinion that we had actually proven a condition in the gouty liver which Schittenhelm and Brugsch had predicted from the results of their clinical work (15). At this time there appeared an article by Wiekowski (18), who was unable to demonstrate uricase in *normal* human organs. We were easily able to confirm Wiekowski's results. An aqueous infusion of liver from a case of aneurism was treated with uric acid and under conditions most favorable to its destruction, but in all experiments a reasonable amount of uric acid could be recovered unchanged. An experiment was also made in which no uric acid was added to the liver extract, but in spite of all efforts to demonstrate uricase a small amount of uric acid was found among the products of self-digestion: so that not only is the human liver incapable of destroying uric acid when added from without, but cannot even destroy the small amount of uric acid formed in a self-digestion from the nucleic acid of the gland (15).

There is, moreover, no demonstrable difference between gout and aneurism, so far as concerns the nuclein ferments, other than uricase (19). As already stated, Schittenhelm and Schmid found all of the nuclein ferments present in aqueous extracts of all human organs, and this observation undoubtedly formed the basis of the theory of gout which Schittenhelm and Brugsch subsequently proposed. The results obtained by Miller and by Winternitz with human organs do not substantiate the findings of Schittenhelm and Schmid. Miller and Winternitz find that, like every animal species thus far examined, the human species has its characteristic ferment distribution.

1. Guanase is easily proved present in all human organs. Relatively large quantities of guanine are rapidly and completely changed into xanthine by aqueous extracts of muscle, spleen, liver, kidney, lung and pancreas.

2. Adenase cannot be proved present in any human organ. Relatively small quantities of adenine can be almost quantitatively recovered after digestion for months with human organ extracts, but a small amount of hypoxanthine can also be found among the products. Whether this trace of hypoxanthine represents a slight activity of adenase, which disappears as digestion proceeds or is entirely apart from the nuclein metabolism, is a question at present in dispute. We have taken the ground that as muscle always contains hypo-

xanthine, which does not come by the action of adenase on adenine, this trace of hypoxanthine constantly found in digested glands may be better accounted for as coming from the small amount of muscle in the glands than as representing the slight activity of an expiring ferment.

3. Xanthoöxidase is in great activity in human liver, but is confined to this organ.

4. Human organs, by their inability to destroy uric acid, differ from the organs of the lower animals.

With matters of disputed interpretation we are not here concerned. In whatever way one is disposed to view the facts they are the same in gout as in aneurism, so that whatever is the cause of gout, it is not a derangement of any of the ferments of the nuclein metabolism, so far as this can be demonstrated with organ extracts.

Shortly after the publications of Wiekowski, of Winternitz and of Miller, Schittenhelm made the following interesting report of his recent examination of human organs (20, 21).

1. Guanase is undoubtedly present in all human organs.

2. Added adenine can for the most part be recovered unchanged after digestion with human organ extracts.

3. Xanthoöxidase is confined to the liver.

4. Uric acid can, to a large extent, be recovered unchanged after digestion with extracts of human organs, but there is some loss. Concerning this disappearance of a small fraction of the added uric acid Schittenhelm remarks that it is too small to be looked upon as evidence of the destroying ferment and too large to represent an analytical loss. It seems a pity that Schittenhelm did not state this last proposition in the form of a syllogism.

The presence in tissue extracts of a small amount of hypoxanthine, which cannot be accounted for as a product of nuclein metabolism, brings us to a discussion of the second method by which uric acid is formed in the animal body.

In the course of his well-known work on the origin of endogenous uric acid, Burian (22) observed that when hypoxanthine is withdrawn from a surviving dog's muscle by perfusion, an equal quantity of the base is produced in the muscle to take its place, so that the amount of this constituent in the tissue thus tends to a constant value. The conditions of his experiments were of course such as to preclude migration of hypoxanthine from any other part of the body. Hence he concludes that the base is being continually formed in the living muscle from some unknown precursor which is not a constituent of the leucocytes. As the amount of hypoxanthine given up to the perfusion fluid was found very much greater after stimulation than after a period of rest, Burian establishes a clear causal connection between muscle stimulation and the production of muscular hypoxanthine.

Hypoxanthine is thus being continually formed in dog's muscle, but as Leonard (23) has shown, dog's muscle extract contains no adenase; nor does the surviving dog's muscle exhibit this ferment (24). Taking into consideration all that we know of the physiology of muscle, it seems fair to conclude that the chemical changes involved in muscle contraction are probably of the same general nature in all muscles. Whether this be rigidly true or not it has been shown that, as is the case with voluntary muscle, the predominating base of involuntary muscle is hypoxanthine, unaccompanied by xanthine, its constant and necessary companion in the nuclein metabolism (25). There seems ample justification for assuming that hypoxanthine is just as characteristic and necessary a muscular constituent as is creatinine or sarcolactic acid. But it is just as true that adenase is not a muscle ferment. Of the muscle extracts of the dog, pig, rabbit, man (26) and ox we have been able to prove its presence only in the case of the last-named species; but the hypoxanthine of ox muscle is not appreciably greater than that of dog's muscle, which latter, by the consent of every one, is practically free from any function that can bring about the formation of hypoxanthine from adenine. Hypoxanthine is not only found with regularity in muscle tissue which does not contain adenase, but in the muscles of certain animal species in which adenase can neither be demonstrated in extracts of any of the organs nor of the combined organs of the entire animal. This is notably true of the rat (27) and is in harmony with Nicolaier's (28) discovery that in these animals subcutaneously injected adenine is oxidized, but reaches the kidneys without disamidization, where it gives rise to deposits of 6-amido-2-8-dioxypurine.

It is obvious that hypoxanthine formed in muscle will be converted into uric acid when it circulates through an organ containing xanthoöxidase, and this is the second method by which uric acid is formed in the body.

A number of considerations lead to the probability that uric acid may be produced in a manner that is different from the two which have been considered. The earlier studies of the nuclein ferments had shown that while one organ does not as a rule contain all of these active agents, yet every species was found supplied, in one organ or another, with the ferments necessary for the formation of uric acid from guanine, from adenine, or from both. But this is not true of the rat (27). The organs of this animal exhibit guanase uniformly and strongly, but the xanthine thus formed is not oxidized to uric acid by any or all of the organ extracts. Yet the rat's urine contains uric acid. The suggestion is clear that this organism has at its disposal some other method of producing uric acid, and this method is indicated in no uncertain way by the brilliant work of a group of Italian chemists under the direction of Ascoli (29).

It has been long known that uric acid is destroyed when an aerated solution of the substance is perfused through the surviving dog's liver. Ascoli now shows that if the perfusion fluid containing the destruction products be saturated with carbon-dioxide and again perfused, uric acid makes its appearance. It will be seen that we are here dealing with two ferment actions, one of which is exerted in the presence of oxygen and destroys uric acid; the other acts in the presence of carbon-dioxide and produces uric acid. But this destructive and producing action are not reversed actions of the same ferment, for, if a bloodless liver be perfused with an oxygenated solution of uric acid the acid is destroyed, while there is no production of the substance upon subsequently perfusing the blood-

less organ after saturation with carbon-dioxide. Again, the destruction products of uric acid by uricase are probably allantoin and urea. The producing ferment forms uric acid from dialuric acid and urea, but not from allantoin and urea. All of the results described can be obtained just as well with organ extracts as with the surviving organs. Uric acid is not produced by carbonated blood nor by an aqueous extract of the bloodless liver, but is produced by a mixture of the two. If the bloodless liver extract be boiled before mixing with the blood, the results are in no way altered; but if the blood be boiled the production of uric acid no longer occurs. Plainly the producing ferment is present in the blood and the organ furnishes the activator, while uricase (also guanase (30)) is found in the bloodless organ extract. Thus uric acid can be formed in the animal body by a process that involves neither a purine ring nor a purine ferment, and this mode of formation has of course received no consideration in any theory of gout.

It is not altogether agreeable to learn that a difficult problem in experimental medicine, once regarded as solved, is again opened to discussion. A degree of satisfaction is to be gotten upon reflecting that an exposed error in science is a double advance, "but we are not here concerned with hopes or fears, only with the truth so far as our reason permits us to discover it: and I have given the evidence to the best of my ability."

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INTRATHORACIC DISPLACEMENTS IN PULMONARY TUBERCULOSIS.*

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The following supplementary report† deals with the changes brought about in intrathoracic relations as shown by skiagrams of cases of pulmonary tuberculosis, studied clinically before and after the taking of the X-ray plate. I will confine myself simply to the more salient features of this study, which deals with the alterations in the position of aorta, heart, and diaphragm. The presence or absence, of enlarged bronchial glands, and of calcareous infiltration of the costal cartilages of the ribs is also briefly considered.

When such a study is carried out with technical precision, it would seem to leave little room for error. Because with the use of the modern tubes and coils, and instantaneous exposures, the resulting skiagrams are so clear cut and definitive as to give an admirable geographical chart. I believe that such a study gives more satisfactory results in regard to the position of the organs in life than those obtained by autopsy, for in the latter there is the post mortem change, due to alteration in intrathoracic pressure or to other strictly post mortem influences, and there is also the trauma of the autopsy and consequent derangement of relations, and finally there is the question of elapsed time. I feel further that purely clinical studies of this nature, when unconfirmed or unchecked by röntgenology, are without much accuracy or value, except in so far as in certain instances the personal equation of the investigator has given them such.

I shall not discuss the use of the X-ray from the standpoint of early diagnosis, nor even in its relation to the later pathological changes. The value of röntgenology in the study of pulmonary tuberculosis, as supplementary to physical examination, is so generally recognized as to need no exposition. Röntgenology must not, of course, be considered as having

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†See preliminary report, entitled: The Effect of Tuberculosis on Intrathoracic Relations, Am. J. Med. Sc., May, 1910. This article contains the case histories in full to which reference is made in the present paper. The author desires to express his thanks here to Dr. A. O. J. Kelly, for permission to publish this supplementary report in the Johns Hopkins Hospital Bulletin.

solved the problems of physical diagnosis of the chest, but it helps to elucidate them and to confirm the clinical findings. It has not and never can supplant nor minimize the importance of the time-honored clinical methods, but on the contrary it should serve a useful purpose in stimulating more exact methods, because the possibilities of physical diagnosis are extended from the information and suggestions gleaned from the X-ray. As Minor has well said in an address before this Society, "it is the corroboration which the X-ray brings to the results of our regular examination that is one of its most valuable features."

The cases from which this study is made, were skiagraphed by Dr. Charles Lester Leonard, of Philadelphia, and were in some instances patients from the Pennsylvania State Dispensary for Tuberculosis (Phila.), and in others, from private practice. The majority of the cases were moderately advanced and advanced cases (Class II and III of the National Tuberculosis Association classification), though the only selection used was in the financial ability of the patient to bear the expense of the skiagrams. The number here reported is too small (that is 81 cases) to warrant me in drawing any very definite conclusions, but the results are at least suggestive, and the conclusions which I do present relate only to this series.

I shall not attempt at this time to discuss the data gleaned from this study in the light of present knowledge or views, but shall content myself with merely recording the details noted, pointing out where in certain instances the conclusions drawn are at variance with the views or opinions of others.

The Aorta and Heart.—It should be noted that quite frequently the aorta is displaced in advanced pulmonary tuberculosis as well as the heart and in the same direction. In marked displacements of the heart this is the rule and such displacement was noted clinically and confirmed by the X-ray in 14 cases. Rarely the aorta may be drawn out of position, while the heart is unaffected. The error is sometimes made of interpreting the physical signs of a displaced aorta as being those of enlarged glands or of aneurismal dilatation. With an area of dulness to the right or left of the sternum in the second or third interspace, with or without expansile pulsation, accompanied by much displacement of the heart, the conclusion that the aorta is displaced is warranted, in the absence of definite signs of aneurism. Rarely an aneurismal dilatation of the aorta may be present.

In 67 per cent of the cases the heart was not displaced (that is in 55 cases). Thus it is noteworthy that in the present series very many of which were advanced or far advanced cases the heart in the majority of instances was not displaced. There seems no doubt about this conclusion, and I therefore feel that those who hold that displacement of the heart is a reasonably constant sign or accompaniment of pulmonary tuberculosis are in error. Turban (1) makes the statement that "it is exceptional to find the heart in its normal position in advanced chronic tuberculosis" while Pottenger (2) says that displacement of the heart is a "typical and cardinal symptom" of tuberculosis of the right apex.

Absence of displacement is much more common, in fact almost the rule, in acute infiltrations and consolidations before fibrosis and contraction have taken place. In many instances even where the lesions were widespread and often destructive, the heart was not displaced. This was true in 25 advanced cases. For instance in a case,[a] with cavitation at the right apex and infiltration of the entire upper lobe, the heart was not displaced due to pericardial adhesions over the apex which could be plainly seen. In a second case,[b] with large cavities in both apices and much fibrosis, the heart was not displaced, possibly on account of the symmetrical character of the lesions, or possibly from adhesions. In a third case,[c] with left sided localized pneumothorax, the heart was not displaced. In a fourth case,[d] with a large cavity on the right side and complete consolidation of the right upper lobe and moderate infiltration on the left side, the heart was not displaced.

There would seem to be three factors which may play a part in preventing cardiac displacement in advanced pulmonary tuberculosis. The first and most important is, of course, the existence of adhesions which bind down the heart; the second, where the destructive lesions are relatively symmetrical in extent, the tendency to displacement to one side or the other seems in certain instances to have been modified and overcome by the equality of the traction exerted on both sides; the third, a left sided localized pneumothorax (which exists more frequently than is generally supposed and is practically always overlooked) may hold the heart in place even in the presence of extensive destructive lesions at the left apex. Thus in one case [e] with a large cavity at the left apex, the heart was much displaced to the left until the development of a small pneumothorax, which forced it promptly back into a normal position. The physical signs of this localized pneumothorax were most inconclusive, but the condition was plainly discernible in the skiagram.

The heart was displaced in 33 per cent of this series, in 15 cases to the right, in 4 cases to the left, in 3 cases upward and to the left and 5 cases in the antero-posterior position to be described later. Thus it was displaced twice as often to the right as to the left. I cannot, therefore, agree with the statement of Lawrason Brown (3) that "marked displacement of the heart occurs much more frequently to the left than the right."

When the pulmonary lesions are of fairly symmetrical character on both sides, the heart if displaced is more commonly drawn to the right than to the left. In these cases there is usually evidence to show that the primary and older lesion is on the right. When the lesion is more extensive on the left the heart is not so regularly displaced nor to the same extent, as in corresponding right-sided lesions. Rarely the fibrosis of

[a] Case XIII.
[b] Case XXIII.
[c] Case XXIV.
[d] Case XXXIII.
[e] Case LXI.

lung and pleura may be so great or of sufficient density to obliterate the boundaries of the heart.[f]

In 5 cases the heart occupied, what for want of a better term I have called the antero-posterior position. In this position the heart assumes a long narrow appearance, as if it were turned upon its vertical axis. It should be noted that in all these cases, there were far advanced destructive lesions on both sides, and it might appear that the combined effect of the traction exerted under these conditions, had resulted in drawing the heart upward and inward, thus causing the apex to swing around. Attention has not, so far as I am aware been called to this very definite position of the heart in certain advanced cases, previous to my description of it in August, 1909.

In long, narrow chests the heart assumes a more oblique position. The angle formed with the liver on the right is less acute and the left boundary is appreciably more vertical. The heart also assumes an appreciably more oblique position during deep inspiration.

In many cases the skiagrams show an interesting feature which is not demonstrable clinically, namely, that during systole of the heart there is an area between the lower boundary of the heart and the diaphragm (a cardio-phrenic space) of about the extent of one centimeter, which distinctly transmits the rays. The limits or extent of the cardiac excursion may also be seen in many cases. In 4 cases, distinct pericardial adhesions could be seen. The heart appeared normal in size both in the X-ray plates and to physical examination, in all the cases with 4 exceptions. In 3 of these the enlargement was practically confined to the right side, and the lungs were markedly emphysematous. In one case[g] there was a general hypertrophy. There was no evidence of an organic lesion in the series, though in some cases soft systolic murmurs were audible in the mitral and pulmonary areas.

The Diaphragm.—The skiagrams were taken under full inspiration. In 41 cases (50 per cent) the diaphragm was unaffected by the pulmonary lesion. In 19 cases it was elevated on the right side, in 7 cases on the left; in 7 cases it appeared to be elevated on both sides; and in 7 cases it was not visible or determinable on account of the density of the adjacent involvement of lungs and pleura.

In every case in which the heart was displaced the diaphragm was elevated on the side toward the displacement, and in the cases where the heart assumed the antero-posterior position the diaphragm appeared elevated on both sides. There was one exception to this rule which does not properly apply as such, but in a case,[h] which had been operated on for left sided empyema, some years previously, there was collapse of the chest wall, with consequent dragging upward of the diaphragm on the left side, while the heart was displaced to the right.

The diaphragm was affected in 18 cases in which the position of the heart was normal. In other words, the diaphragm was more sensitive to, or affected by, the presence of a pulmonary lesion than the heart in 19 per cent of the cases. This was true in 11 advanced cases, as well as in 6 of the earlier cases, and yet in 10 advanced cases where one would have expected to find the diaphragm affected, it was not apparent (except in limitation of pulmonary excursion), either to physical examination or in the plates. Thus in cases[i] of relatively slight involvement the diaphragm may be elevated on the affected side; while in cases[k] with marked involvement and even cavitation the diaphragm may not be elevated but in these cases the heart is not displaced. Thus the diaphragm had responded, in change of position, to the pulmonary lesion in half the cases.

The Peribronchial Lymph Nodes.—In every case in this series the cervical glands were enlarged to palpation. It would seem probable that the peribronchial glands are also affected in all cases, though this could not be deduced from the skiagrams. In 59 per cent of the cases enlarged glands could be seen in the plates. With the exception of about 20 cases all the cases in which enlarged glands were visible were either relatively early or moderately advanced, without marked breaking down of tissue; while in the majority of the far advanced cases the glands did not show. It would appear as if there might be two explanations for the absence of glands in the majority of plates in which they were not visible, namely, that their presence was concealed by the area of involvement, or what appears more likely, that with the advance of the disease the glands had softened or broken down and so failed to give rise to a shadow. There were usually only three or four glands or clusters of glands noted in any one plate, and in a number of instances they appeared to be calcified.

Calcification of the Costal Cartilages.—The presence of calcareous infiltration in the costal cartilages was noted in only 12 cases. It would appear to be grossly absent in many cases in which its presence might be expected and where it could no doubt be demonstrated microscopically, and it was generally noted in the advanced chronic type of the disease, though there were exceptions to this. It was usually confined to the costal cartilage of the first rib, though in several instances it involved them all. In many of the advanced cases the involvement was of sufficient density and extent to have concealed the presence of calcification in the cartilages of the first rib, but there was no calcification in the costal cartilages which could be properly studied.*

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[f] Case IX.
[g] Case XIX.
[h] Case XXVII.
[i] Case XXII, as type.
[k] Case XIII, as type.

* The summary of each case with classification and details of lesions will appear in a final report.

BLOOD CULTURES IN PNEUMONIA.

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The more recent blood-culture studies in acute lobar pneumonia have led to the general conclusion that in most cases, at least, the disease must be regarded as a general pneumococcæmia. But the results have been so discordant that the question cannot be considered definitely settled. Some investigators have reported growths in 90 per cent or more of their cases; while others obtain them much less frequently. Numerous reasons have been advanced to explain the varying results. We have attempted to investigate some of the points in controversy in a small series of cases from the medical clinic of the Johns Hopkins Hospital, which we are allowed to report through the kindness of Professor L. F. Barker.

The blood was obtained from the median-basilic vein in a sterile syringe of 15 cc. capacity, and was placed in culture media directly at the bedside. The media employed in each case and the degree of dilution are indicated on the chart. The medium called "special" was a 10 per cent peptone, 2 per cent glucose water, made up according to the directions of Wiens (1), who reports better results with this than with any other media. Cultures made in 1 to 10 dilution were in test tubes; the higher dilutions were in flasks.

Of 25 cases studied, cultures of the pneumococcus were obtained from the blood of 14; i. e., in 56 per cent. In the series, 5 cases were fatal (20 per cent), and in all these the cultures were positive. Of the 14 positive cases, 36 per cent died. In 7 of the positive cases, a second culture was taken after the crisis or during lysis, but no growth was obtained. An analysis of the 11 negative cases shows that in 4 (16, 18, 20, 22) the cultures were taken on the day of the crisis; in 3 (17, 24, 25) on the day preceding the crisis. Cases 15 and 18 were unusually mild. Cases 19 and 23, however, were more severely ill than many of the positive ones.

As soon as growth was discovered in the cultures, transfers were made to blood agar slants. In every case but one, growth was evident within 18 hours. Every culture was examined carefully at the end of 24 and 48 hours, both microscopically and by making transfers to blood-agar slants before being reported negative. Capsules were easily demonstrated in every case. Further studies of the cultural characteristics identified the organisms as pneumococci. In one case the thick, watery growth on agar, the arrangement in chains, and the easily staining capsules indicated the variety commonly known as *Streptococcus mucosus capsulatus*. Tests of the phagocytability of the organisms by normal human serum and leucocytes were made immediately after isolation. In every case the organism was not phagocytable.

The media used in each case, and the dilution, are given in detail on the chart. In but two cases were agar plates employed. In Case 3, one to three colonies appeared on each plate. In Case 4 no growth was obtained in any medium at the first culture. In all cases some of the following media were used: litmus milk tubes and flasks, broth tubes and flasks, glucose-broth flasks and Wiens' special 10 per cent peptone, 2 per cent glucose water in tubes and flasks. The dilution of the blood was determined in each case. Most of the cultures were at a dilution of 1 to 10, and 1 to 30; but growth was obtained at a dilution of 1 to 5, and of 1 to 75. In the series of positive cases, the milk tubes showed no growth in two, and Wiens' special medium also was negative in two. Plain broth gave growth in 7 of 9 cases, and glucose broth in all of the 10 cases in which it was used. On the whole, it may be said that when obtained at all the pneumococcus grew about equally well in all the liquid media. The examination of the cultures has to be made promptly, for in many cases it was found that the culture died out after 48 hours.

From so small a series as this no final conclusions can be drawn. Two points, however, may be mentioned: (1) positive cultures were obtained in 56 per cent of the cases of an epidemic in which the mortality was only 20 per cent; and (2) the organism was easily obtained.

Prochaska (2, 3), in Zurich in 1901-1902, obtained positive cultures in 100 per cent of his cases. In his series of 40 cases, the mortality was 20 per cent. Many of them were mild. He used liquid media in varying dilutions, finding agar unsatisfactory. He obtained growth in 2 cases one day after crisis, and in 1 case two days after crisis.

Rosenow (4, 5), in Chicago, reported 91 per cent positive cultures in a series of 175 cases, with a death rate of 40 per cent. As a medium he used broth (chiefly) in a dilution of from 1 to 50 to 1 to 75. The percentage of failures to obtain a growth was higher during the 36 hours preceding the crisis than earlier in the disease, although he obtained growth in a few cases as late as 48 hours after the crisis. He also obtained growth 12 hours after the initial chill, before signs appeared in the lungs.

Kinsey (6), 1904, in Chicago, made a parallel series of cultures; in one using 8-9 cc. of blood in 50 cc. bouillon, with growth in 12 per cent; in the other, using a dilution of from 1-15 to 1-20, with growth in 76 per cent. His death rate was 32 per cent. He concludes that pneumococci are present in all cases, and that technical difficulties sometimes prevent their isolation. He finds as the most suitable method the use of liquid media in a dilution of 1-15 or 1-20.

In contrast to these results are those of Schottmüller (7),

Case No.	Sex.	Color.	Age.	Day of Disease.				Blood Culture.					Remarks.
				Admission.	Crisis.	Lysis.	Death.	Day of disease.	Days before recovery or death.	Media.	Dilution.	Results.	
1	M.	W.	43	8	.....	.....	10	9	— 1	Special	1—25	+	Extreme toxæmia. Autopsy.
										Gluc. broth	1—75	+	
										Milk	1—10	+	
										Special	1—10	+	
2	F.	B.	43	11	.....	.....	18	13	— 5	Gluc. broth	1—20	+	Acute ulcerative endocarditis. Meningitis. Abscess of lung. Autopsy.
										Milk (2).....	1— 5	+	
										Broth	1— 5	+	
3	M.	B.	50	1	.....	.....	7	4	— 3	3 agar plates...	1— 5	+	Streptococcus peritonitis, following appendicitis. Operation. Pneumonia 3 days after operation.
										Milk	1—10	+	
										Gluc. broth	1—30	+	
										Broth	1—10	0	
4	F.	W.	(?)	.....	.....	.....	.....	.....	.....	3 agar plates...	.....	0	Meningitis. Patient entered hospital at the end of pneumonia with pulmonary signs still present. Date of onset not known.
										Bile	.....	0	
										Milk	.....	0	
										Special	.....	0	
										Gluc. broth	.....	0	
										Gluc. broth	1—30	+	
										Special	1—30	+	
										Special	1—10	+	
										Milk	1—10	+	
5	F.	B.	44	5	.....	.....	10	6	— 4	Broth	1—30	+	After 24 hours all negative. At 48 hours broth flask +. After 72 hours milk tube +.
										Special	1—30	0	
										Special (2).....	1— 5	0	
										Milk	1— 5	+	
6	M.	B.	24	4	10	.....	.....	5	— 5	Broth	1—40	+	Temperature about 100° F. at second blood culture.
										Special	1—25	+	
										Milk (2).....	1—10	+	
										Special	1—10	+	
								13	+ 3	Same media	.....	All 0	
7	M.	B.	25	6	.....	10–18	.....	8	— 2	Gluc. broth ...	1—30	+	Pneumonia migrans.
										Special	1—30	+	
										Milk	1—10	+	
										Special	1—10	+	
								16	.....	Same media	.....	All 0	
8	M.	B.	25	6	.....	15	.....	8	— 7	Milk	1—30	+	
										Gluc. broth	1—30	+	
										Milk	1—10	+	
										Broth	1—10	+	
										Special	1—10	+	
								20	+ 5	Same media .. .	.....	0	
9	F.	B.	20	3	.....	.....	.....	4	.....	Milk	1—30	+	Empyema 32d day. Signs on admission obscure. Diagnosis by blood culture. Gluc. broth + 18 hours. Milk + 3 days.
										Gluc. broth	1—30	+	
										Broth	1—10	0	
										Milk	1—10	0	
10	M.	B.	24	2	12	.....	.....	3	— 9	Milk	1—30	+	
										Gluc. broth	1—30	+	
										Special	1—10	+	
										Milk	1—10	+	
										Broth	1—10	+	
								14	+ 2	Same media	.....	All 0	
11	M.	W.	40	4	.....	8–10	.....	4	— 4	Gluc. broth	1—30	+	Second blood culture on 3d day of normal temperature.
										Broth	1—10	+	
										Milk	1—10	+	
										Special	1—10	+	
								13	+ 5	Same media	.....	All 0	
12	M.	W.	18	2	.....	9	.....	3	— 6	Special	1—30	0	Empyema 14th day.
										Special	1—10	+	
										Special	1—10	0	
										Milk	1—10	Cont. animat'd	
								12	+ 3	Same media	.....	All 0	

Case No.	Sex.	Color.	Age.	Day of Disease. Admission.	Crisis.	Lysis.	Death.	Blood Culture. Day of disease.	Days before recovery or death.	Media.	Dilution.	Results.	Remarks.
13	M.	B.	20	3	.....	8–38	.....	5	— 3	Special	1—30	+	Delayed resolution. Temperature 99.5° F. at second blood culture.
										Gluc. broth	1—30	+	
										Special (2)	1—10	+	
										Milk	1—10	+	
								15	.....	Same media	.....	All 0	
14	M.	B.	21	4	12	.....	.....	5	— 7	Broth	1—75	+	Blood 5 cc.
										Milk	1—10	+	
										Special	1—10	+	
								13	+ 1	Same media	.....	All 0	
15	M.	B.	26	1	5	.....	.....	2	— 3	Gluc. broth	1—30	0	Unusually mild case.
										Milk	1—10	0	
										Broth	1—10	0	
16	F.	W.	32	7	.....	7–9	.....	8	0	Gluc. broth	1—50	0	Blood 5 cc. Taken during lysis.
										Milk	1—10	0	
										Broth	1—10	0	
17	M.	W.	17	7	9	.. ..	.....	8	— 1	Milk	1—30	0	Otitis media, 16th day.
										Gluc. broth	1—30	0	
										Milk	1—10	0	
										Broth	1—10	0	
18	M.	B.	24	3	9	.....	.....	4	— 5	Milk	1—30	0	Continued slow pulse. Respiration 24. Very mild case.
										Gluc. broth .	1—30	0	
										Broth	1—10	0	
										Milk	1—10	0	
								9	0	Same media	.....	All 0	
19	F.	W.	12	3	... .	.....	.....	4	.....	Gluc. broth	1—30	0	Pseudo crisis on 6th day. Interlobar empyema. Operation 22d day. Pneumococci in pleural fluid.
										Milk	1—10	0	
										Milk	1—30	0	
										Broth	1—10	0	
								16	.....	Gluc. broth ...	1—30	0	
										Milk	1—30	0	
										Milk	1—10	0	
										Broth	1—10	0	
20	M.	W.	34	9	.....	10	.....	10	0	Gluc. broth ...	1—30	0	Case from North German Lloyd Steamer.
										Milk (2).....	1—10	0	
										Broth	1—10	0	
										Special	1—25	0	
21	M.	W.	18	3	.....	(?)	.....	4	—	Gluc. broth	1—30	0	Indefinite physical signs. Broncho pneumonia (?) Very gradual fall in temperature. Case from North German Lloyd Steamer.
										Milk (2).....	1—10	0	
										Broth (2).....	1—20	0	
										Special	1—25	0	
22	M.	W.	25	5	5	....	.....	5	0	Broth	1—30	0	Blood culture on day of crisis.
										Broth	1—10	0	
										Special	1—10	0	
										Milk	1—10	0	
23	M.	W.	1	.....	8–22	.....	.....	2	— 6	Same as 2d culture.	.....	0	Parotitis.
								4	— 4	Special	1—25	0	
										Milk	1— 5	0	
										Broth	1— 5	0	
										Special	1— 5	0	
										Special	1— 5	0	
24	M.	B.	18	4	7	.....	.....	6	— 1	Special	1—50	0	Culture taken day before crisis.
										Broth	1—50	0	
										Milk	1— 5	0	
										Special	1— 5	0	
										Broth	1— 5	0	
25	M.	B.	27	5	7	.....	.....	6	— 1	Gluc. broth	1—50	0	Post critical rises up to 14th day. Temperature 100° F. at second blood culture.
										Special	1—40	0	
										Special (2).....	1—10	0	
										Milk	1—10	0	
								9	+ 2	Same media	.....	All 0	

of Hamburg (1905), who obtained only 23 per cent positive cultures in a series of 209 cases. He used agar, making seven plates out of 10 to 20 cc. of blood. He obtained one positive result on the day of crisis. He got growth only in severe cases and considers a positive culture of bad prognostic value. He made comparative tests of liquid and solid media, and does not think technical difficulties explain the difference between his results and those of Prochaska: sarcastically remarking that "if Prochaska got such constantly positive results, then the explanation must be that pneumonia in Zurich behaves differently from pneumonia in Hamburg."

Similarly low results were obtained by Cole (8), in this clinic in 1900-1901. He reported only nine positive cultures (30 per cent) from a series of thirty cases with a mortality of 43 per cent. He used 10 to 15 cc. of blood; and as media, milk and broth in flasks, "in order to dilute the blood further, and so to overcome the bactericidal effect of the blood." He got positive cultures only in fatal cases, though not in all of these; and considered a positive culture as of bad prognostic value.

Wolf (9) (1906) emphasized especially the presence of the organism in the circulating blood after crisis. In 16 cases positive before crisis 6, or 37 per cent, were positive after crisis; 3 in uncomplicated cases 8 hours after crisis; and 3 in cases of delayed resolution, 7, 16 and 17 days after the fall in temperature; 1, one day, and 1, two days after normal temperature, and 1, three days before temperature became normal. The organisms obtained were not phagocytable by normal human, dog or guinea pig leucocytes in normal serum, or by the leucocytes and serum of the convalescent cases from which they were isolated, and were as virulent for rabbits as were the precritical organisms from the same patient. Wolf concludes that crisis cannot be associated with a sudden disappearance of organisms from the blood or with a change in their virulence.

Wiens (l. c.), in Breslau (1908), reports a series of 33 cases with 79 per cent positive results in which the death rate was 18 per cent. Several cases were positive during the fall of temperature at the beginning of crisis or lysis, and one case was positive one day after crisis. Two were positive the day before crisis. He concludes that bacteriæmia is constant in pneumonia if proper fluid media are used, and lays stress on his 10 per cent peptone, 2 per cent glucose water.

The following conclusions may be drawn from a summary of these reports:

(1) In certain epidemics blood cultures in pneumonia are positive in a majority of all cases.

(2) In such cases the results have no prognostic value.

(3) Pneumococci may be obtained at times from the blood of patients after crisis.

(4) The failure to obtain organisms in the blood is due in part to technical difficulties, in part to other factors.

These reports also furnish some basis for speculation as to the nature of the other factors causing the still varying results in the study of this question. The pneumococcus is an organism very susceptible to environment. A vigorous growth in one medium may not reproduce itself when transferred to media of other composition. This is especially true of cultures in milk, which may be very active and yet may not grow at all when transferred to blood agar, an equally good culture medium. The uncertain viability of the pneumococcus may also be inferred from the assertion of Rosenow (l. c.) that he was able to demonstrate the organism in smears from the blood of pneumonia patients from whom he could not isolate it by cultural methods. Aside from the slight differences in culture media, which in making cultures from the blood appear to be of little importance, it would seem the explanation must be either that the infective agent is not identical in all cases, or that the changes it undergoes in the human body vary greatly.

One point that possibly may have some significance, though hitherto neglected, is the matter of locality. Thus, acute articular rheumatism, a disease resembling pneumonia in many respects, varies considerably in its manifestations in different places. What is apparently the same disease is seen under quite different aspects in London and Baltimore. In other infectious diseases a similar difference in behavior may be noted in different places and at different times. It would seem possible that in pneumonia differences in the infectious agent itself, due to environment, or to locality, might play some part in explaining the difference in results of blood-culture studies in Chicago and Zurich, from those in Baltimore and Hamburg. However, in the absence of any experimental proof of such differences, such an explanation must be regarded as a mere speculation.

Nor can it be dismissed with the simple statement that improvement or recovery is necessarily associated with the absence or disappearance of the organisms from the blood. It is important to recognize that, although the pneumococci generally disappear from the blood before crisis, virulent organisms may be demonstrated in some cases even after the temperature has become normal. Yet it seems quite probable that the explanation may be found in some change (possibly a slight one) in the organisms themselves, produced perhaps by the antibodies, or defensive forces of the host. Experimental studies on pneumococcus infections in animals tend to show that the result of such infections depends on the balance acquired between the forces of the invader and the antibodies of the host, both of which may be present at the same time, as Mancini (14) has recently shown by the method of deviation of complement. Crisis or lysis will occur when the cause of the disease is overpowered by the resisting forces of the body, but, as Wolf maintains, without necessarily implying the death of pneumococci in the blood. Thus it is not difficult to conceive that in pneumonia the living organism might be present in the blood, but not always in such a condition as to grow when transferred to ordinary culture media.

We wish to acknowledge our indebtedness to Dr. Rufus Cole for valuable suggestions and actual assistance in the preparation of this report.

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MEMORIAL SERVICES FOR ISABEL HAMPTON ROBB, WHO DIED APRIL 15, 1910, AT CLEVELAND, OHIO.

A large number of the friends and associates of Isabel Hampton Robb assembled in the parlors of the Nurses' Home, at the Johns Hopkins Hospital, on Sunday afternoon, May 8, 1910, to do honor to her memory.

REMARKS OF DR. HENRY M. HURD, SUPERINTENDENT OF THE JOHNS HOPKINS HOSPITAL.

Several weeks ago, when we learned the sad news of the death of Mrs. Robb, there was a general feeling that we ought to take some immediate method of showing our appreciation of her work, and our great grief at her loss. It was thought best under the circumstances to have the simple service of the church that she loved so well. Accordingly, three weeks ago to-morrow a service wholly of a religious character was held in this room, which proved most comforting to all who were present. At that time, also, it was decided that as Mrs. Robb's work here had been of an epoch-making character and her memory was so dear to all, it was requisite we should have a more formal commemoration of her eminent services at this hospital, where she did the best and most enduring work of her career.

While sitting here I call to mind how on the 9th day of October, 1889, Miss Hampton, afterwards Mrs. Robb, made her first appearance in this room before a Baltimore audience, which had gathered at this time to signalize the opening of the training school for nurses connected with this hospital. Previous to that time the nursing work in this hospital had been carried on in a hand-to-mouth fashion, satisfactorily, upon the whole, as we had excellent nurses, but without special system. Each nurse had been trained in a different school and there was necessarily a lack of co-ordination and order. The hospital had been only partially opened and many important departments had not yet been organized; consequently up to this time it had not been possible to establish any training school. Miss Hampton came to Baltimore a few days prior to the first of October, but did not begin her duties as superintendent of nurses and principal of the training school until the date above mentioned. As the title indicates, she was not only superintendent of nurses, but also principal of the training school, and had charge of the education of the nurses, and her position as principal of the training school gave a recognition at once to the fact that she was engaged in the work of teaching.

I remember well the audience that gathered here on that October day to hear Mrs. Robb. There were Francis T. King, so many years the president of the board of trustees, to whom we owe this building, and who had very just ideas as to what proper nursing should be; also George W. Corner, who died only a short time ago, one of our oldest trustees; Judge George W. Dobbin, Judge Geo. William Brown, Dr. Alan P. Smith, C. J. M. Gwinn and Francis White, of the board of trustees. There were Lewis N. Hopkins, the nephew of Johns Hopkins; also Mrs. Miles White, his only surviving sister, and Henry D. Harvey, one of his business partners. There were President Gilman, Prof. Remsen, Cardinal Gibbons, Mayor Latrobe, Dr. James Carey Thomas and others. I might mention many others, but these will suffice to show the character of the audience present. Mr. King made an address, which was followed by a paper from Mrs. Robb, giving an outline of what she intended to accomplish in establishing the training school. In that paper she set a standard which has been adhered to ever since and which has had much to do with the success of the training school. What she said was so appropriate and gave such a good conception of what she wanted in a trained nurse, that I will read a few sentences:

Schools for nurses, in fact, consider little that is sentimental and much that is practical, in deciding upon the fitness of a woman for nursing. While some may have more natural aptitude for the work than others, there are other attributes quite as important that are required.

Training schools aim to receive only women who are at least fairly intellectual, the more so the better results, who are strong and enduring physically, and who morally will recognize the sacredness of the work that they are engaged in. Of their pupils training schools require that they shall yield implicit obedience and loyalty to the physician, that they shall faithfully carry out his directions, and in his absence watch over the welfare of his

patient, and further his scientific study of disease by intelligently fulfilling his orders in administering medicines, taking account of the range of pulse and temperature, regulating the sanitary condition of the sick room, noting every unusual symptom in the patient, keenly alive to its importance, and reporting the various changes in his condition, as the patient responds to treatment.

Thus by night or by day a nurse must be on the alert; she must have at her command presence of mind to meet any emergency, must abound in tact and patience with those suffering from mental disturbances, and be unwearying in her efforts for her patient's comfort; and all this and much more she must do cheerfully, being kind and sympathetic and adaptable to the varying necessities of the sick room.

I do not know but that this might have been expressed more concisely, but it certainly would not have given as fully Mrs. Robb's ideal of the true nurse and of the mission of the training school.

Mrs. Robb was with us for a period of five years. She brought order out of confusion and established a system of instruction which has gone on with increasing usefulness ever since she left us to marry in 1894. She did not give up her interest in the training school, but was always anxious to know of its welfare and prosperity. It was her conception of the teaching function of a training school which induced her to urge upon our trustees, even after she had left the school, the importance of establishing an eight-hour day, the importance of providing paid teachers and the importance of giving the pupils of the training school as much opportunity for study as they had for practical work. I think that these contributions to training school work were pre-eminently hers. She saw clearly the importance of giving instruction of a character suited to improve the intellectual capacity of the nurse, to increase her capacity for effective work, and finally to fit her to be not only a nurse but a teacher.

When she went to Cleveland, she showed a similar interest in hospital and training school affairs. I will, however, leave to others to give some account of her life there, as they know it much better than I do. Her personality commanded respect and affection. When you met her you were in contact with a generous nature and a personality with large ideas and broad views of her duty to the world and especially to the sick and suffering. I believe very few persons have ever been in this hospital who have left a better or more enduring impression. It is a pleasure to think of the women she trained: Miss Nutting, Miss Nevins, Miss Ross, Miss Barnard, Mrs. Thayer, Mrs. Finney and others. I could name many others, who worthily have carried on the work she began so ably and so nobly. We all owe a debt of gratitude to Mrs. Robb for her work and for the workers she has inspired.

I wish to ask Miss Nutting, as her successor, to give some account of her work and I would express the hope that she will speak at length.

Remarks of Adelaide Nutting, Professor of Hospital Economics, Teachers College, New York City.

I have been asked to speak to you this afternoon of the educational work of Isabel Robb, the great woman who organized this training school, established its standards, shaped its traditions, and placed it upon the basis educationally which has enabled it to hold for nearly twenty years a leading place among the great training schools of the world. That it has attained this high rank has not been due primarily, I believe, to the fact that it was connected with a hospital affording large and unusual opportunities, with costly buildings and elaborate equipment, and that we were connected with a noted university; other schools have these; but it has been due to Mrs. Robb's insistence from the beginning upon the importance of maintaining and developing the educational side of nursing work. At this moment we are too near her to give any just estimate of her work, and in this spot, so crowded with memories of her, it is difficult to speak at all, the more so, because, great as she was in her work, splendid as have been the influences and inspirations which have flowed from it, it is not at this moment the teacher, the organizer, the leader, whom we have lost and mourn, but the beloved woman, with her gracious ways, her radiant vitality and irresistible charm, her almost childlike delight in the beautiful and pleasant things of life, her warm human impulses, and even her human imperfections. For these things she is close to our hearts, and it is with an effort that we turn from them to pay tribute to her fine achievements through which alone in the future she will be known and honored, which are her imperishable contributions to the world.

I had the privilege of close and constant association with Mrs. Robb from my earliest days as a pupil in this school, and a friendship began then which has been one of the strongest influences of my life. Many times have we talked together of her home life and education, her training at Bellevue and her work in Chicago. Her upbringing was in a home of Spartan simplicity, and her mother, an English woman of the old school, had strong ideas of duty and discipline and of the part they played in the training of children. The daughter in the home had clearly defined duties and responsibilities, and Mrs. Robb often spoke of the value of the training in these very practical duties in her home, the performance of which was always rigidly insisted upon. She received on the whole an unusual education, remaining at school until about twenty years of age. She thought of teaching or of studying medicine, but the way did not seem to open, and eventually she entered Bellevue Training School, in New York, where she soon became intensely interested in nursing, discerning in it a work of great possibilities.

Upon her training in Bellevue Mrs. Robb frequently dwelt, and in teaching constantly drew for illustration upon the experiences which the hospital offered in such variety and abundance. The working day of the pupils ranged from 8 a. m. to 8 p. m. with, it was stated, one hour off for dinner, and "additional time for rest and exercise." Many conditions combined to make those hours off an uncertain and variable quantity. The wards were full of very sick patients, and the number of nurses to care for them small. There were many evenings, too, when the work could not be finished at the stated hour of 8 o'clock, and when her pupils remained on until a

later, sometimes much later hour, obtaining in some small shop in the vicinity the supper they had missed.

Attendance at lectures was not compulsory, if the needs of the patients were unusually urgent. The pupil could remain in the wards, or the head nurse could keep her there during lecture hour, and thus such theoretical instruction as was provided could be lost altogether.

Finally it came about that a little group of pupils, Mrs. Robb one of them, felt so greatly the need of further instruction that they gathered together in one of their rooms at night, after work was over, and carried out regular courses of study, as systematically arranged as the nature of their lives would permit. I remember particularly hearing Mrs. Robb speak of the regular classes and quizzes in anatomy and physiology which they tried to conduct, with the hope of acquiring a sounder knowledge of the human bodies they were caring for, in order that they might do more intelligent work over them. Often has Mrs. Robb assured me that her ideas as to the needs in the education of nurses grew out of her own experience, in finding herself confronted with conditions and situations in nursing for which little or nothing in her training had prepared her. Yet she never for a moment undervalued the kind of power which that training at Bellevue brought her, though she felt keenly the need of a sounder and better educational policy as a matter of justice to the pupil and to the work into which her hospital training inevitably led her.

I am inclined to think that at that time the pupils were sent out into private families during some part of their second year, for the stated purpose of acquiring experience not to be obtained in a municipal hospital.

On leaving Bellevue, Mrs. Robb spent a few weeks at the Woman's Hospital, and then joined other graduates of her school at St. Paul's House, in Rome, an institution established under the auspices of the American Episcopal Church, for the purpose of providing suitable nursing in illness for English and American visitors. I have often felt that here was her first contact with the beautiful things of the world, that the beauty and glory of life first dawned upon her in Italy. Over and over again in the evenings she would bring forth her cherished collection of photographs, and dwell upon the memories of her days there, as something very rare and precious which she had always with her.

At the end of a year and a half Mrs. Robb returned to America, and soon after went to Chicago, to take charge of the Illinois Training School for Nurses, connected with the Cook County Hospital, a very large municipal institution whose political control made conditions difficult to cope with. The training school was not, however, a part of the hospital, but was, and still is, under an independent body, a board of women managers. With their support, interesting developments were made in the work of the school.

Perhaps the first instance of an affiliation for an educational purpose was when this training school undertook to do the nursing in a large neighboring hospital—the Presbyterian—which offered in its private service additional and desirable opportunities for the pupil nurses. The lectures and other theoretical instruction in this school, as in most others at that time, had been limited to the first year, owing to the prevailing custom of sending pupils out into families to nurse during their second year. Mrs. Robb saw the advantages of continuing the instruction into the second year, and in carrying out this idea aimed unconsciously an effective blow at the common policy of sending out pupils.

Those who were associated with Mrs. Robb in Chicago very soon came under the influence of her wonderful personality, and to their admiration for her strong and progressive work, added a devotion which time and absence have not been able to impair.

In little less than four years the Johns Hopkins Hospital was completed and opening its doors and its training school, and from a number of candidates for the position of superintendent of nurses, Mrs. Robb was chosen. Here she found her great opportunity. Here was a new field, unmatched in its resources, rich in its possibilities, free from trammels of precedent or tradition, offering her freedom to work out her ideas and plans in an atmosphere sympathetic and helpful to an unusual degree, and here she did her greatest and best work.

From the very beginning she emphasized her desire to uphold educational ideals and standards in insisting that her title should be not only that of superintendent of nurses, but also principal of the training school. It is just a little pathetic to look back and remember that in the effort to give us as pupils some better instruction than was commonly offered in training schools, it was arranged that we should have two lectures a week of one hour each.

After a brief trial this had to be dropped; it was too advanced for the time. The lectures came in the evening, and while we could struggle through one in the week and work up our notes, two proved entirely impossible.

I have often heard Mrs. Robb speak of the diet school in a hospital as its one purely educational feature, in that the services the pupils might render to the hospital in it were the secondary, and not the primary, consideration.

While the opportunities were unusual, those first years of work presented many difficulties. In organizing the work it was necessary to bring in as heads of wards and other departments graduate nurses from various schools and from different countries. They not only differed widely in standards and ideals, but had been trained in methods so diverse that to produce a desirable uniformity or harmony in the system of training seemed well-nigh impossible. There were some excellent head nurses, women of fine powers and unswerving in their allegiance, yet it was no uncommon thing for us to be taught certain methods in the class-room by Mrs. Robb, and upon our return to the wards to find these methods questioned, and to be directed to use others.

To maintain unity and steadiness of purpose amidst the confusion wrought in the mind of the pupil by such conflicting influences required great patience and insight, and it has always seemed to me a striking evidence of Mrs. Robb's remarkable power that she was able to do it. I think few heads of schools have ever gathered about them a more devoted group

of pupils. We were filled with loyalty which could not be shaken. Constantly she held up to us the highest ideals in our work, placing before us unceasingly the importance of nursing and the great responsibilities which rested upon those who undertook it, urging that they must always be women of exceptional character and ability. She filled us with great pride in our work and a desire to contribute to its best development in all ways open to us. It seemed to us better worth doing than any other work in the world.

Notwithstanding the wide sweep of her vision, she was nevertheless one of the most practical of women. I have often been struck by the simplicity and the practical nature of her plans when they came to the sifting point. The measures she suggested were as a rule such as could be carried out. Sometimes they were large measures, but they were not often impracticable.

A noticeable feature of her character was her love of uniformity. I have often felt that there must have been a long line of military ancestry in the background to account for her ideas on this subject and on that of discipline. We were an army—we must work as an army—must keep step—must not get out of line—our standards must be uniform. It was, therefore, a matter of profound satisfaction when she was able to fill every post in the hospital and school with graduates whom she had trained, and could feel that a uniform system of teaching and training was established throughout the place.

At the end of five years Mrs. Robb had not only thus completed the organization of the work in school and hospital, but had during that period written and published her text-book of nursing—and then she left us.

In the fifteen years since that date, while still meeting fully the cares and responsibilities of home and family life and many large social demands, she steadily maintained her interest in nursing affairs, and her contributions to professional development have been noteworthy. As a member of the board of managers of Lakeside Hospital, she was happy in giving largely the results of her practical experience, and I have heard from the trustees and her co-workers there how greatly they relied upon her judgment and wisdom.

She was eager to see the development of a good system of visiting nursing in Cleveland, aided in its establishment, and was an enthusiastic supporter of its work, and I cannot think that she ever failed to respond in her own community to whatever call was made upon her in which nurses, hospitals, the care of the sick, or the prevention of sickness were concerned.

The Society of Superintendents of Training Schools owes its first impetus to her and the little group of seventeen heads of training schools with whom in Chicago in 1893 she discussed the formation of a society of such workers to advance educational standards and bring about uniformity of methods. That has now grown to a large society of 360 members.

Throughout all the years she has steadily attended the meetings and prepared papers, and only last year she was its president. The society about ten years ago appointed a committee of which she was chairman to study possibilities for the training of teachers of nursing, and the work of this committee eventually led to the establishment of courses at Teachers College, which have just grown into the dignity of a department —that of nursing and health.

Mrs. Robb was among the lecturers to the students of this course, and her last visit to New York, in January, was for the purpose of fulfilling such an engagement.

Of the Associated Alumnæ she was the first president, and carried it through its early difficult years of organization.

From the very beginning Mrs. Robb realized fully the value of the printed word, and her views, plans and suggestions were unfailingly embodied in some paper or report where they were, as she herself said, "on record." In addition to her two well-known books, "The Principles and Practice of Nursing" and "Nursing Ethics," which are in general use in training schools all over the country, there are among her writings several papers and addresses which I have long felt ought to be more widely available than they now are. I asked her last January if she would not soon gather together a collection of such writings, and from her reply I found that she was arranging for their publication, which we may hope will be soon. They will form an invaluable contribution to the literature of nursing, and we shall hold them among our most cherished possessions.

During the winter we have been preparing for a celebration of the Fiftieth Anniversary of the founding by Florence Nightingale of the first training school for nurses, and had asked Mrs. Robb, as one of our pioneer workers, to give an address on that occasion. She wrote, regretting that the pressure of many matters compelled her to decline, but as we were not willing to accept her refusal, after a few weeks I wrote again, begging her not to fail us. I had not heard from her when the appalling news of her death called me to Cleveland, but in talking with Dr. Robb, he told me of a few scattered notes which he had found in her desk, referring to nursing education under the title which we had named. So it seems that her last work for nurses was an effort to respond to our request that her voice and presence should not be lacking on an occasion of such unusual importance, and we know now that she was unwilling to fail us.

In all my knowledge of her I can hardly think of a time when questions of nursing were not uppermost and seemingly matters of vital interest. In her teachings, in her writings, in her practical contributions, and in her public activities she held up firmly and consistently ideals in nursing and in the education of nurses which compelled respect and attention and which in the general upbuilding of standards in a new field of women's work will be found ultimately to have been of quite incalculable value. Every year that passes will but add to our gratitude for her gifts and devotion to her memory.

Remarks of Mrs. William M. Ellicott, of Baltimore.

It is as my father's daughter, as well as the friend of the wonderful woman we have lost, that I would like to say a word this afternoon. It was my father's earnest desire that this training school for nurses should be a model in the United States, and I remember well his coming home one day and say-

ing, "I have found an administrator." Certainly we all know, from the fruitful results of Mrs. Robb's labors, that he had found an administrator; and from that time on it was one of his greatest pleasures to confer with her, and to listen to and encourage her admirable plans. She has often said to me, "I owe much to your father, because he appreciated all my efforts and always encouraged me;" and she nursed him so faithfully in his last illness that from that time on my friendship for her was so deep that I can harly speak of it now.

I feel that we cannot put a measure to the indebtedness which the profession of nursing owes to her; but I also feel that, as women, we owe much to her. Her type of womanhood was very remarkable: the serene look in her blue eyes told always of difficulties to be faced and conquered, never to be worried over, and whenever there was hard work to be done, she either went forward and accomplished it, or, if this were impossible, she laid it aside until it could be freely taken up again. Her example has made her the friend of all women, and we know that she has left behind her an ideal which, wherever we are working and wherever we are living, will be felt as the type of true womanhood. For her to have been snatched from us in her supreme vigor and maturity is perhaps to leave to us the most perfect memory of her; and I appreciate this opportunity to add a tribute to her from all the women of America.

REMARKS OF DR. LEWELLYS F. BARKER, PROFESSOR OF MEDICINE, THE JOHNS HOPKINS UNIVERSITY.

It is a very great privilege for me to be here and to be allowed to say a few words on this occasion. In the early years of my acquaintance with Mrs. Robb I had a very high regard for her, and as I learned to know her better that regard grew into a very strong friendship that increased with the years.

I want to speak about her death and burial. It is rather remarkable that her death should have been due to something quite out of accord with the main tenor of her life. Most of you have heard the details of that horrible accident in Cleveland, when, in a moment of curious indecision, she failed to cross the street and was caught between two cars and crushed to death. Usually easily able to decide promptly, she had for years had a sort of psychic indecision about that one matter of crossing the street; and she had spoken to many of her friends of her fear that she would sometime be killed by a street car. It is very remarkable that this psychic fear should have been well founded. Such an apprehension is almost never realized, but in this one instance unfortunately it was.

Mrs. Robb was Canadian born and was always most loyal to Canada and Great Britain, and although she did not expect to be buried in Canada she had often expressed the wish that this might be. After her death her husband, in order to carry out that wish, sent one of his best friends immediately to Canada to arrange for her burial in the spot which she had indicated; but unfortunately conditions were found to be unsuitable, and word was sent back strongly advising the postponement of the interment until better arrangements could be made. Dr. Robb himself then went to Canada and made an investigation personally, and felt so keenly the disadvantages of the local conditions that he appealed to some of us here, asking for advice and help. I talked with Dr. Hurd and with others about it, and we felt strongly that under the circumstances it was much better to have her interred at Burlington, New Jersey, her husband's home, where the conditions were very satisfactory and where her grave would be accessible to many, especially to nurses who might wish at some time to visit it. I mention this that those of you who may have been aware of her wish to be buried in Canada may know why that wish was not carried out.

I would like to say a few words about some of the qualities of mind and heart of her whose memory we are meeting to-day to honor. I think the first point that should be emphasized is her energy. The more I see of men and women the more I realize the importance of great energy well directed, and this Mrs. Robb had in superabundance. She gave the impression of the embodiment of energy. She did not easily show fatigue, and in her teaching work and her relations with others it was largely this force and activity in which she abounded that made her so strong and so helpful.

A second point is her enthusiasm. As Miss Nutting has emphasized, she was most enthusiastic in everything she undertook: for the time being it was her whole life. And she had the courage of her convictions. I have never known any woman more ready to stand boldly in the face of opposition for the point which she wished to make. As soon as she felt convinced that it was right she went ahead with it and fought for it, and it was not her fault if the point was not gained. But with her courage and enthusiasm there was always a deep sense of justice and right, and if she could be convinced that the thing which she had in mind was not for the best she was ready always to yield. In her dealings with nurses this faculty of justice was a noticeable one. Many nurses have said to me that they felt that Miss Hampton was always just, that though sometimes the decision seemed hard, there was always a good reason for it. Her sense of justice and right has been a matter of praise among all who knew her.

As to her relation to the training school I shall say very little—so much has been so well said by Dr. Hurd and Miss Nutting. I shall refer only to one point, and that is what she accomplished in raising the social status of the nurse. And this is a point which I think deserves emphasis, for I believe that largely through her influence—at first here, in the beginning of this training school—the social status of the nurse has been elevated to a very high degree throughout the whole country. When you think of the difficulties that stood in the way of a better class of women in training schools, when you think of the women she chose to be nurses and of those who have succeeded them ever since in this training school, when you think of the influence that such standards have had upon the choice of women in other training schools, then you will begin to realize that the social elevation of the trained nurse in America is one of the great contributions of Isabel Hampton. We of the medical profession appreciate this particularly,

because it has made it possible for the nurse to co-operate with the physician in a way which before had been entirely impossible. If a nurse is intelligent, refined and cultured and if she has charm, she can do for her patients something which is quite out of the power of one who does not possess these qualities. We realize this very keenly, and are always glad of an opportunity to point out this contribution which the Johns Hopkins Hospital Training School for Nurses, largely through the influence of its first superintendent, has made.

Another and a very pleasant side of Mrs. Robb which I had the opportunity of seeing, was as wife and mother. She has bequeathed to her two boys sound bodies and sound minds, and I am very glad that they have had her as an influence in their lives for at least as long a period as she was with them.

Hers is certainly one of the most notable personalities that the profession of nursing has offered to America and to the world; and these qualities that I have mentioned, of energy, enthusiasm, courage, justice and idealism, we may well keep in mind and carry away as lessons that her life has taught.

Remarks of Miss Georgia M. Nevins, Superintendent of the Garfield Hospital, Washington, D. C.

Just a word in behalf of that first class, and to mention a few points in Mrs. Robb's character that strongly impressed me all the years that we worked so closely together not only in the school, but since that time. If by any chance there is a feeling among the later pupils that the members of that first class have a very good opinion of themselves, it is far from true, for we realize that opportunities for the benefit of the pupils have increased every year over the advantages which we may have had; but it was a wonderful privilege to be under the direct and constant supervision of such a woman as Miss Hampton. She came here filled with enthusiasm and high ideals and soon selected the first class of seventeen. There was but one text-book for nurses at that time and all the teaching, practical and otherwise, was done by herself personally—only possible in those very early days of the hospital.

The quality of her work must have been indelibly impressed upon every one of her pupils. "The comfort of the patient" was emphasized always as our first consideration, and her faithful teaching of every detail of nursing has left an impression so vivid that, to this day, I rarely take a class without being reminded of her. Trained in Bellevue at a time when it was difficult to obtain the necessary comforts for patients, she developed a resourcefulness and knowledge of economy which proved most helpful to those of her pupils who later took charge of institutions less fortunately endowed than this. Her power of observation seemed very remarkable to young pupils. I remember one instance, when as a probationer, I had been told to put a room in order, which I thought I accomplished to perfection; Miss Hampton came into the room, and in a flash espied a tiny cobweb hanging from the chandelier, when, of course, my spirits fell. Another incident illustrates her intense interest in her work and its results. When I first took charge of the Garfield School, Miss Hampton came over frequently to see how her child was getting on. We had with us a graduate of this school on special duty. Miss Hampton came upon her in the corridor one day, and I am sorry to say that, without a cap and with her handkerchief carelessly worn instead of a collar, she did look rather untidy. A greeting over, the nurse passed on, when Miss Hampton's face flushed, her eyes filled with tears and she exclaimed: "Have I worked for this?" She was pained beyond description that her teaching was so soon forgotten.

Mrs. Robb's almost childlike interest and enthusiasm in so many different ways was truly remarkable. Within one hour I have known her to be absorbed in the outline of the new preliminary course which we were to take up in the school, and in the next, she was just as interested in sewing lace on a baby's dress. Rarely is a woman endowed with such superb physical strength and great dignity. We found her very firm, upon occasion, but always eager, full of the joy of living, and we can never forget her fascinating smile and the gentle voice which it is impossible to believe is forever still.

I have been asked to speak of Mrs. Robb's work in connection with the Red Cross. She was interested from the beginning of the Red Cross reorganization, and wished to see a large enrollment of the best nurses of the country, to be called upon in the event of war or other emergency needing their services. She was asked by the Red Cross Central Committee to outline a system of enrollment. This she did, and while her plan could not be carried out altogether, on account of the expense, it led to the present organization through the State and local associations of graduate nurses.

One word more: We may hold meetings in her honor, portraits may be painted, but it seems to me that there can be no monument to Mrs. Robb equal to the influence in the world by the graduates of this school, if we carry out the principles and ideals of our first superintendent, Isabel Hampton Robb.

Remarks of Dr. William H. Welch, Professor of Pathology, the Johns Hopkins University.

I am sure that everything possible has been said to indicate our esteem and appreciation of Mrs. Robb's work. There is only one other point that perhaps may need to be emphasized. If there is one thing more than another distinctive of the medical work in this place it is that all the forces concerned have worked together as a unit—the university, the hospital, the medical school and the training school for nurses. The influence which has been attained is due in very large measure to this co-ordination and harmony, and I regard the work of the training school as one of the most important contributions of this place, from the medical side, to the country. The interest which attaches to Mrs. Robb's association with the work is that kind of interest which always goes to a pioneer, to the one who has begun things which have become important; and her name, therefore, will always be a name to be treasured, not only here, but throughout the country.

I perhaps knew Mrs. Robb slightly earlier than anyone here, as I was one of the lecturers to those hard-worked nurses at the

Bellevue Hospital. I recall very vividly going down in the early days to the Bellevue Training School at half-past eight at night, and those weary, tired nurses coming in and sitting in a row for me to talk to for an hour. I used to welcome their nodding heads, for I felt that then at least I was doing some good. Mrs. Robb has herself occasionally referred to this experience.

Now the Bellevue Training School was, of course, a pioneer in the work of nursing in this country, but Miss Nutting, in her very interesting and admirable survey, has pointed out in what respects it was defective—especially in the long hours and the very meager character of the educational side of the work. Therefore, I may speak for all of my colleagues in the medical school when I say that we are very proud of our training school and that we are very proud of those who have made it such a success. It stands, in its own sphere, toward the profession of nursing as eminently as the medical school and the hospital do in their respective provinces. Now one must have some understanding of the value of the profession of nursing in modern medicine to appreciate how significant and important a contribution it is in the whole field of medicine and also to the community at large. It has changed the face of modern medicine; it is revolutionary in its influence upon the progress of modern medicine. We can hardly imagine ourselves back in the days when the trained nurse did not exist, but we can imagine what a backwoods, and even medieval, state we would be thrown into if we had not this great arm of medicine to lean upon. Commensurate in importance are the problems connected with the education of the nurse, for they are not all settled to-day. They are large problems; and hence the work of one who contributes to them is a large and important work. Mrs. Robb, therefore, did not work in a small corner; hers was not work relating to a very restricted and limited field; but it was work which pertains to one of the most important developments in medicine, and indeed in social reform, of the day.

Miss Nutting has admirably indicated the general features of Mrs. Robb's work here in the training school, and I shall, therefore, only point out that the hospital was most fortunate in securing her services. She proved to be the one best adapted to initiate and carry on this work, by her forceful, charming and attractive personality and by her excellent qualities of mind and heart. We were, therefore, singularly favored in having her with us at the beginning of the training school. Her work marked a very important era in development. It has stood, and stands to-day, for certain ideals—ideals which are not universally accepted by others—ideals that there is no such thing really as over-education of the nurse, but that a nurse—as Dr. Barker has so well pointed out—is all the more of service the better her general education and her qualities of heart and of character. These are, in part at least, the ideals which I think we may say that the training school of the Johns Hopkins Hospital has introduced.

Those of us who were here in the beginning when the hospital was opened count Mrs. Robb among the group who started things here, and I venture to say that as long as this hospital endures her name and her work will be among its most cherished possessions.

Isabel Adams Hampton Robb was born at Welland, Canada, in 1860. She received her education at the Collegiate Institute, St. Catherine's, Canada, and in 1881 entered the Training School for Nurses connected with Bellevue Hospital, New York, and was graduated from there in 1883.

Following her graduation, Miss Hampton spent a short time in private nursing, and was then appointed Head Nurse in the Woman's Hospital of New York City. She resigned this position to go to Italy, where for nearly two years she nursed in connection with St. Paul's House for Trained Nurses in Rome.

In July, 1876, she was appointed Superintendent of the Illinois Training School for Nurses associated with the Cook County Hospital in Chicago. During the three years of her service there she brought about the affiliation of the Presbyterian Hospital with the Cook County Hospital in the matter of nurses and made notable improvements in the method of training nurses.

When the Johns Hopkins Hospital was opened Miss Hampton was chosen as Superintendent of Nurses and Principal of the Training School for Nurses and entered upon her duties October 1, 1889.

In May, 1894, Miss Hampton resigned her position at the Johns Hopkins Hospital and in the following month was married at St. Margaret's Church, Westminster, London, to Dr. Hunter Robb, formerly of Baltimore. In November of the same year Dr. and Mrs. Robb went to reside at Cleveland, Ohio, and there their two sons, Hampton and Philip, were born.

In Cleveland she maintained an active part in nursing affairs and became a member of the Board of Lady Managers and Chairman of the Training School Committee of the Lakeside Hospital.

She was also the promoter of two prominent nursing organizations in this country, "The Society of Superintendents of Training Schools," and "The Associated Alumnae of Trained Nurses," and was instrumental in founding "The American Journal of Nursing." The course in Hospital Economics in the Teachers' College, Columbia University, was largely the outcome of her efforts.

In recognition of her work in presenting the need of well-trained nurses to the Red Cross Society, she was made a member of the War Relief Board of the National Red Cross Society. She was also a member of the Matron's Council, London, England, and was appointed delegate to the last International Congress of Nurses.

In addition to numerous papers and addresses, Mrs. Robb was the author of three books: "Nursing, its Principles and Practice, 1894"; "Nursing Ethics, 1900"; "Educational Standards for Nurses, 1907."

IN MEMORIAM.

CAMILLUS BUSH.

On Saturday, May 28, 1910, Dr. Camillus Bush, of the class of 1902, Johns Hopkins Medical School, died at the Adler Sanitarium in San Francisco. He had been ill for about three weeks, suffering from typhoid fever; but a double pneumonia, which developed during the third week, was the immediate cause of death. He was buried at his home in Woodland, California.

Those who knew Camillus Bush in Baltimore have felt that their appreciation of his rather unusual traits of character should receive some adequate public expression, and have desired to record their feelings in THE JOHNS HOPKINS HOSPITAL BULLETIN.

We should be untrue to his memory if our affection for him should lead us into any extravagant estimate of his worth; for he fled from flattery; and while he was quick to recognize real excellence in others, he was always discriminating in praise and frank in criticism. The attitude of sincerity which he maintained toward others, he was glad to have others maintain toward himself.

He came to this Medical School from the University of California; and he brought with him the rugged virtues of pioneer ancestors. From the first he shunned publicity, but his quick mind and ingratiating ways soon made of him a marked man. He made many and strong friends in the Medical School and in the city. His few antagonisms were equally strong and equally creditable to him. To his medical work he gave intelligence and devotion. The facility with which he absorbed information, and the ease with which he acquired skill were the admiration and envy of those who worked with him.

His service in the Johns Hopkins Hospital as interne and as Assistant Resident Surgeon fulfilled the promise of his student days. His chief interest was always in the clinical side of medicine; and his hospital days first gave him the opportunity for the exhibition of easy, but faithful, acceptance of responsibility, tactful and thoughtful care of patients, keen surgical insight and excellent surgical judgment which promised so much for his success as a surgeon. When Bush left Baltimore the affection of every one with whom he had come in contact went with him; and it is well within the limits of moderation to say that no one who has served the Hospital has been more widely loved than he.

In San Francisco he met with unusual success. In spite of great discouragements at the first—emphasized by his undaunted devotion to high ideals which refused to accept compromise that would have made progress easy—in spite of a somewhat uncongenial medical atmosphere, he rapidly forged to the front; and though only 32 years of age, and but 8 years in practice, he was at the time of his death one of the most promising young surgeons of his city: competing, and competing successfully, with men of years and experience, and widely admired and respected by the profession.

He was a man of unusual integrity. His professional conscience was like a knife-edge. He saw with a keen eye the daily petty compromises with ideals which longing for success forced men around him to make; but no such compromises, not even the most trivial, entered into his own programme of life. Indeed, those who were interested in his early San Francisco days rather feared that he might be over-doing his assertion of independence; but his candor and honesty finally won for him the respect of the profession; and though he never made any efforts—not even the most respectable—to force a practice, patients, and patients in good numbers, soon found him out and sought his aid.

He was a man, too, of unusual ability. Things came easily to him; and this facility almost led him at times to an intolerant attitude toward those who found difficulty in their work. But he was quick to discern and generous to praise excellence in others. He felt no particular call to the productive side of research in medicine; but he was keenly alive to all that was being done in this direction. He set an excellent example by keeping out of work for which he did not feel himself fitted, and by maintaining an attitude of intense and freely expressed disgust for the pseudo-scientists who interpret research as self-exploitation. He was an excellent operator, had sane surgical judgment, understood the sympathetic care of patients and accepted his work with a due sense of responsibility.

He was a man of unusual charm. His outlook on life was fresh and boyish, his fondness for life deep and his belief in its essential excellence strong. His alert mind, ready wit, shrewd eye for human frailties, whimsical way of putting things and constant cheerfulness made him the very best of companions. He not only enjoyed life himself, but was the cause of its enjoyment in others. These excellences of his character were by no means casual. They were the expressions of a nature essentially serious, essentially spiritual—for Bush had a faith almost naive in its intolerance of doubt, a faith for which "all sorts of proof were impertinent"; and many who had seen only the fun-loving, lighter side of his nature would be surprised if they knew to what an extent this belief shaped and dominated his career and what sacrifices he made for it.

Men of Bush's type are not born every day. The city where he worked and the profession which he served need such men. Those who have known the delight of intimacy with him, mourn him with a deep and sincere sense of personal loss.

J. W. C.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS MEDICAL SOCIETY.

March 21, 1910.

Dr. Louis Hamman presiding.

I. The Effect of Diminished Blood Supply to the Intestines upon the General Circulation. Dr. W. T. Longcope, Philadelphia, Pa.

To be reported in full in the September number of the Johns Hopkins Hospital Bulletin.

II. The Morphological Reaction of Certain Nerve Cells in Functional Activity in Relation to Surgical Shock.[1] Dr. D. H. Dolley, Chapel Hill, N. C.

The changes in size and in the nucleus-plasma relation in the Purkinje cells formed the basis of discussion. The sequence of the changes in chromatin content, previously published in a paper by Dr. Dolley, was summarized to show the correlation with the size changes. The findings were based on the measurements of two thousand two hundred cells and nuclei. The material came from five dogs, one normal, one exercised in a treadmill, and three shocked to death by intestinal manipulation. The use of three fixatives to control the results divided the data into eight series. In each series, the chromatin changes were separated into eleven main, and subsidiary stages, so far as they appeared according to the severity of the experiment, and the figures and curves presented were based upon the average for the most part of twenty-five cells to each of these stages, though in one case fifty, and in the normal seventy-five were taken. The sizes were calculated in actual volume figures.

With the transition to activity, the size of both cells and nuclei increases along with the progressive hyperchromatism. Before the maximum hyperchromatism is reached, the size begins to diminish, and with the regressive hyperchromatism declines through the shrunken cells first depicted by Hodge. From this minimum, the size of both elements increases with the onset of edema to the last stage measured in which the karyosome alone remains of basic chromatin.

The nucleus-plasma relation remains constant up to the maximum of enlargement with hyperchromatism. In the light of the work of Hertwig and his associates, this finding was regarded as very significant in delimiting strictly normal activity. The size of both elements increases but in the same ratio. From this point, the nucleus decreases relatively more, so that the relation comes to be progressively in favor of the cytoplasm. The onset of edema in the nucleus before the cytoplasm brings about a shift in the relation in favor of the nucleus, which reaches its maximum at the point where the cell is passing through the semblance of normal in its chromatin reduction.

Then the factor of edema in the cytoplasm begins to turn the balance the other way and to the end the relation is progressively in favor of the cytoplasm.

From these facts deductions were made regarding the mechanics of nerve-cell activity, bringing the changes in size and chromatin into relation. The hyperchromatism was explained as being a disturbance of the equilibrium in favor of chromatin formation, an initial overactivity on the part of the nucleus. When, however, the consumption of extra-nuclear chromatin comes to exceed its formation, there results a functional hypertrophy in the relatively more strained nucleus, so that the relation comes to be volumetrically in favor of the nucleus.

This accords with Hertwig's idea that the result of functional activity is first a disturbance of the balance in favor of the nucleus, for in the stage of hyperchromatism the nucleus is to be judged by the external measure of its activity in extra-nuclear chromatin. Following the nucleus, the cytoplasm becomes hypertrophic, and the visible result of the enlargement of both is the secondary outpouring of chromatin which follows the exhaustion after the onset of fatigue. Finally as a result of the increased demand on the part of the cytoplasm, depending on the greater diminution of nuclear activity, the relation comes to be disturbed in favor of the cytoplasm, and the natural limit is reached in actual dechromatinization of the nucleus.

In conclusion, from the inherent significance of a purposeful character in the changes, from the analogy with an obviously physiological condition such as muscular exertion, from the practical application to various functional states shown by differential counts, and from the agreement with accepted manifestations of activity, the changes are held to be the morphological expression of functional activity in the type of cell considered. In the case of such shock as was experimentally induced, its effects appear to be essentially the manifestation of varied states of activity, overactivity, fatigue and exhaustion in nerve cells. The symptomatic expressions are to be referred to the degree of the reaction and to its manner of localization.

April 4, 1910.

Dr. Louis Hamman presiding.

I. Disturbances of Peripheral Cardiac Innervation in Acute Infectious Diseases. Dr. C. F. Hoover, Cleveland, Ohio.

Dr. Hoover reviewed several observations made by himself and his colleagues on the alteration of heart-rate and blood-pressure as a result of pressure on the vagus nerve. In one or two instances this pressure was digital and made by the observer and the characteristic changes in the pulse-rate and blood-pressure were noted. In the remainder of the cases the pressure was brought to bear on the intra-thoracic portion of the vagus by pathological processes involving the mediastinal glandular tissue and the lungs themselves.

One case in particular, which was confirmed by autopsy

[1] To appear in full, under the title "The Pathological Cytology of Surgical Shock," in the Journal of Medical Research, XXII, No. 2.

showed the effects of pressure on the vagi. This case was that of a young girl, aged 12 years, who for several months had paroxysmal attacks of asthma. These attacks were of very short duration and during the intervals between attacks, the patient suffered no embarassment of the respiratory or circulatory system.

During one of these attacks the patient died and at autopsy, a large mass of caseous tuberculous glands was found in the thorax and running through the midst of these glands both the vagi and the phrenic nerves were found.

The second case reported was a remarkable one of arterial hypertension. This patient, a woman of 40 years, had been suffering with angina for over 15 years and when admitted to the hospital showed a blood-pressure (radial) of 350 mm. of mercury. Marked difference was made out in the blood-pressure in the femorals as compared with that in the radial arteries. There was no enlargement of the heart and the patient did not experience any pain on percussion at the edge of the area of cardiac dulness which Dr. Hoover believes to be present in cases of early cardio-vascular disease.

There was no fall in blood-pressure evident, when patient was asleep.

II. Multiple Carcinomata Arising from the Branchial Cleft and their Differential Diagnoses from other Malignant Lesions in the Neck. Dr. J. C. Bloodgood.

Carcinomatous growths in the neck, with certain restrictions represent a favorable and curable form of carcinoma. Unfortunately the great difficulty in these cases lies in the apparent inability of the physician to convince the laity that an early surgical intervention is possible. In the great majority of cases the patients come into the surgeon's hand at a stage, too late for surgical measures.

In nineteen cases of multiple carcinomata arising from the branchial cleft, studied both from a clinical and surgical aspect, the following interesting facts have been noted:

Only two cases occurred in individuals under 40 years of age. The remainder of the cases were in patients between 40 and 70 years of age. In but two exceptions the duration was less than two years.

The principal symptom of onset was that of a "palpable and movable tumor in the neck." Pain served as an early symptom in but few of the cases. Stiffness of the neck was the most common complaint. No etiological factor seems evident, trauma was offered in but one of the cases, while the "extraction of a tooth" was thought to be the causal factor in another case. This form of tumor may have the same situation as a benign atheromatous cyst. It is important to keep in mind that growths in the neck presenting redness, swelling and abscess formation may be one of carcinoma formation, which have broken down.

April 18, 1910.

Dr. Rupert Norton presiding.

I. Recent Views on the Production and Destruction of Uric Acid in the Animal Body. Dr. Walter Jones.

See third article in this number of the Bulletin.

II. Report of Pathological Specimens. Dr. E. K. Cullen.

Dr. E. K. Cullen reported a series of gynecological cases and exhibited drawings and pathological specimens.

Case I.—*Combined adenocarcinoma and mixed-cell sarcoma of the ovary.*—This tumor occurred in an unmarried woman fifty years of age. The tumor originated from the left ovary. It measured 15 x 14 x 7 cm. On gross examination it presented a definitely malignant appearance. On section of the tumor it was impossible to state whether the growth was a carcinoma or a sarcoma; for in some places it resembled the former, while in others it showed a typical picture of the latter. On microscopic examination it was found to be a mixed tumor, showing a definite adenocarcinoma with a stroma of mixed cell sarcoma. In some areas the carcinomatous process was more prominent, while in others only a few atypical glands were seen in a mass of typical sarcomatous tissue. Such tumors occurring in other organs (uterus and thyroid) have been reported, but a careful search of the literature for a similar tumor of the ovary was unsuccessful. There were no metastases found at operation. At the present time, however, some months after operation, the patient shows signs of local recurrence.

Cases 2 and 3.—*Sarcomatous transformation of myomata.*—These two cases showed early sarcomatous change in myomata. In Case 2, the change was so early that it was overlooked on gross examination.

Case 4.—*Extensive adenocarcinoma of the body of the uterus; myomata uteri; tuberculosis of the left Fallopian tube; and parovarian cyst on the left side.*—This case was especially interesting on account of the multiplicity of pathological processes present. The association of the carcinomatous and tuberculous processes is especially interesting. Careful examination of the stroma of the carcinoma adjacent to the tube showed no evidence of tuberculosis.

Case 5.—*Primary carcinoma of the appendix.*—The history of this case was that of chronic appendicitis. The appendix was 9 cm. in length and averaged 9 mm. in diameter. There was definite thickening of the distal third of the appendix, and on section the lumen was found to be almost obliterated. Malignancy was not suspected on macroscopic examination. On microscopic examination, however, a section taken through the appendix close to the tip showed a definite adenocarcinoma which involved almost the entire thickness of the wall.

Serial sections were made, and it was found that at the tip the carcinomatous process involved the entire wall, but at no point did it penetrate the mesentery. As one approached the central portion of the appendix, however, the process became limited to the mucosa and the lumen. Sections taken from the central and proximal portions of the appendix showed only slight round-celled infiltration of the submucosa.

May 16, 1910.

Dr. Rupert Norton presiding.

I. Experimental and Clinical Illustrations of Dyspituarism. Drs. H. Cushing and E. Goetsch.

For a full discussion of these experiments the reader is referred to a paper under title of Experimental Hypophysectomy in Bulletin of The Johns Hopkins Hospital, May, 1910, Vol. XXI, No. 230.

II. On the Action of Various Antimony and Arsenical Compounds in Experimental Trypanosomiasis. DRS. J. J. ABEL and L. G. ROWNTREE.

Some sixty different varieties of trypanosomes have been found up to the present time and almost as many supposed remedies for this disease have been claimed by their respective discoverers.

In the main those compounds showing trypanosomicidal virtues are compounds of arsenic and antimony. Since the introduction of the "atoxyl" compound by Thomas, this substance has been tried with countless changes and modifications. The term "atoxyl" seems misleading, since certain toxic effects and untoward symptoms have been noted after long continued use of this drug. The antimony compounds appear to be much less toxic in their action than the arsenic compounds. Dr. Abel finds that it is easy to cure small animals, such as rats, in experimental infections of trypanosomiasis. Treatment must be begun soon after infection has taken place.

Protection against the disease seems absolute when the drug is given at the time of the inoculation of the animal. Twenty-four hours after an intra-peritoneal inoculation of the animal, the course of the disease may be stopped by the giving of the drug. Even at the end of three days (72-78 hours) after inoculation, at which time the animal usually succumbs to the disease, administration of the drug causes a prompt recovery. Relapses may occur, but these cases promptly respond to treatment. Of 104 rats, all of which received an experimental infection, 41 are still living and a large number of those dying were undoubtedly killed by overdosing at an early stage in the experiments when the proper size of the dose had not as yet been established.

But few experiments have been tried on the other laboratory animals, such as dogs and cats, and much work has still to be done along these lines.

III. The Toxicology of the Tutu Plant. DR. W. W. FORD.

Tutin, tutu, or the toot poison is the active principle of several species of Coriarieæ, a group of plants found especially in New Zealand. On account of the serious pecuniary loss through the many deaths which occur in stock from eating these species, this plant has received much attention of late years.

The Coriarieæ are small shrubs or small trees and both their succulent branches and delicious berries are eaten with avidity by the domestic animals. The native Maoris have been familiar with the poisonous character of these plants since early times and from their language the term "toot" or "tutu" is derived.

The various species of Coriarieæ are identical in their poisonous action and no animal is naturally immune. Cattle and sheep especially suffer most severely, but larger animals are also susceptible. Owing to the widespread knowledge of the deadly character of the plant and its ease of recognition the number of cases on record of poisoning in man is not large, perhaps some twenty to twenty-five in all.

In animals poisoned by the plants the symptoms are largely referable to the nerve centers and consist of increased respirations, tetanic convulsions and coma. These symptoms usually make their appearance within a short time after eating and lead to death of the animal in a few hours. In man recovery from severe poisoning occurs, but impairment of memory may result. Very many remedies have been tried but without marked success. Bleeding is a therapeutic procedure which has received much favor by the stock owners and in cases of poisoning in human beings this has been combined with the use of stimulants, emetics, compulsory exercises and chloroform to control the convulsions. Lime, carbonate of ammonia, and other alkalis have proven effective remedies in the hands of some of the investigators.

"Tutu" the active principle may be obtained from the juice expressed from the finely divided young shoots of the plants. After filtration and evaporation to a thick syrup, it is then neutralized by sodium bicarbonate and a crystalline deposit is obtained upon recrystallization; the crystals are colorless, odorless and in shape oblique-ended prisms. The compound is volatile, has an intense and lasting bitter taste and gives the chemical reaction of a glucoside. That is it reduces Fehling's solution only after inversion by mineral acids, but then very strongly. It has the percentage composition of $C_{17}H_{20}O_7$. It is highly toxic, 0.129 gram killing a pig weighing 17 kilos in 5 hours, 0.01 gram killing a kitten weighing 1 kilo in 40 minutes and 1 milligram causing a severe illness with convulsions in a cat of average weight.

Dr. Ford has subjected this compound to many exhaustive tests and has ascertained the following additional interesting facts. Tutu is a poisonous crystalline compound to which immunity cannot be produced. It is itself very resistant, it can be boiled without destruction and must be hydrolized with strong acids before it gives off its sugar molecule. In its resistance to heat it may be compared to some of the snake venoms.

Tutin solutions preserve their toxicity for long periods of time without apparent deterioration.

In animals dead from tutin intoxication it is possible to locate the poison accurately in the nerve structures to which it is closely bound. The poison may be identified by its chemical reactions.

THE LÆNNEC SOCIETY.

March 31, 1910.

Dr. Rupert Norton presiding.

I. Intra-thoracic Displacements in Pulmonary Tuberculosis. DR. ALBERT P. FRANCINE, Philadelphia.

See second article in this number of the BULLETIN.

II. Demonstrations of X-ray Findings in Pulmonary Tuberculosis. DR. CHARLES L. LEONARD, Philadelphia.

The study of pulmonary tuberculosis by the Roentgen rays has extended over most of the period since their discovery. The air-filled lungs showed in marked contrast to the sur-

rounding structures upon the fluorescent screen. In consequence the fluoroscope was first employed in the study of pulmonary tuberculosis. With it more rapid progress could be made because at that time viscera in motion could be observed that could not be roentgenographed.

Roentgenoscopy has, however, never afforded more than a rough method of visually confirming the findings of other methods of physical diagnosis. It lacks the essential elements of clear detail and mechanical registration which give accuracy to the roentgenogram. It yields visual, fleeting images that can only be compared mentally with the normal or other pathologic images.

The roentgenogram made while the patient held the breath showed the fallacies of the roentgenoscopic method. The instantaneous roentgenogram by eliminating all motion has rendered the fluoroscope valueless, or only of slight secondary importance, so that it is being abandoned by its most ardent advocates, and only used where the number of examinations make accuracy of secondary importance to the time and expenses incurred.

Improvements in apparatus and advances in technic have made possible exposures of one-fourth of a second and less, and have thus eliminated the motion due to the heart's pulsations. Stereo-roentgenograms made with these short exposures possess a detail and give a power of observation that render roentgenoscopic observations crude and valueless.

The advance to instantaneous stereo-roentgenography affords an opportunity of observing the pathological changes in the tuberculous lung, that is limited in value, only by the ability of the observer to differentiate the pathological from the normal. It gives, by mechanically registering the changes present, the opportunity for study, by numerous observers, of any one case; the repeated comparison of each case with the normal, with other pathological findings in other cases, and with other observations of the same case.

The value of this method is therefore dependent upon the ability of the observers to translate what is to be clearly seen. As in all other methods of diagnosis, the personal equation enters and the value of the diagnosis must depend upon the ability of the observers to translate the facts elicited. This method, however, possesses the advantage that the data secured are mechanically registered and can be submitted to any number of observers.

It compares favorably with a microscopic section or pathological specimen, and has the advantage, for the patient, that it is antemortem evidence.

The Roentgen method of examination can only show macroscopic lesions, which are recognizable as variations from the normal. It can in no way suggest their etiology. Since it cannot determine the cause it can only be used to suggest, confirm, amplify and render more accurate and permanent the findings of other methods of physical diagnosis. This method will often show lesions which cannot be determined by the physical signs but are suggested by the symptom-complex. It will determine more accurately the position and extent of all macroscopic lesions. Thus enlarged peribronchial glands and deeply situated areas of infiltration and consolidation can be shown which cannot be recognized by other methods of physical diagnosis.

Although this method by itself is incapable of establishing an early diagnosis of pulmonary tuberculosis, it often adds definite evidence of pathological change to a clinical picture which lacked confirmation by physical signs. It thus assists in forming an earlier diagnosis than could have been made without it.

In the later stages of the disease it gives more accurate information regarding the size and position of areas of infiltration, consolidation, softening and cavitation, while outside the lungs it localizes areas of pleural effusion or of pneumothorax. It is particularly with reference to the changes in position of the heart and greater blood-vessels that this method has produced an increase in our knowledge. The relative height of the two sides of the diaphragm has played a prominent rôle in the fluoroscopic study of pulmonary tuberculosis. The study of the positions and displacements of the mediastinal viscera shows that the changes in their position affect the relative capacity of the two lungs more than the variations of the diaphragm.

The presence of early adhesions of the pleura and pericardium to the diaphragm have been shown, with variations in the position of the heart causing rotations upon its axis until an antero-posterior position has been reached, or marked dextro-cardia with, in extreme cases, a displacement of the entire aorta with the heart.

Another pathological change frequently noted has been the calcification of the costal cartilages. The connection between this change and pulmonary tuberculosis has not been demonstrated, but the question arises is it the result of limited motion, or as the author has suggested in a previous paper, possibly a process of anchylosis to limit motion, such as accompanies tuberculous arthritis.

In the stereo-roentgenogram more minute detail can be perceived. The size, form and relation of infiltrated areas to the cavities which they surround is defined more clearly in three dimensions. More minute glands can be distinctly seen as glands; dilated bronchi can be noted, and the displacements of the viscera readily estimated with the adhesions which occasion them.

In the lantern slides which follow and the negatives as shown in the stereoscopes will be seen the demonstration of the points summarized above.

III. Influence of Menstruation on the Course of Pulmonary Tuberculosis. DR. DAVID I. MACHT.

This paper will appear in full in a later number of the BULLETIN.

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